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Surgical Treatment of Ruptured Abdominal Aneurysms

Factors Influencing Outcome

RONALD J. STONEY, M.D., AND EDWIN J. WYLIE, M.D., *San Francisco*

■ *The preoperative course and the postoperative results in 44 patients with ruptured abdominal aortic aneurysms were analyzed with particular emphasis on determining the reasons for the continuing high mortality rate. It was found that rupture was usually a process of staccato progression in pathologic events and a deteriorating clinical course. In cases in which the diagnosis was suspected and operation was performed soon after rupture, the risk was not significantly greater than that of elective aneurysmectomy. When operation was delayed until shock was established, the mortality rate rose precipitously.*

APPROXIMATELY HALF OF the patients operated upon for ruptured abdominal aortic aneurysm die during or soon after operation.¹ In spite of increasing experience, no significant reduction in the mortality rate has been made in the past 12 years.¹ However, during this 12-year period the mortality rate for *elective* aneurysmectomy in a series of 510 operations at the University of California Medical Center has dropped from 15 percent to less than

5 percent. To analyze the factors responsible for the high risk of emergency operations on ruptured aneurysms, the case records of patients operated upon for aortic rupture were reviewed. From this analysis it is hoped that principles in management can be formulated which will decrease the operative risk.

Clinical Material

Forty-four patients with ruptured abdominal aortic aneurysm were admitted to the University of California Medical Center, San Francisco, between July 1, 1957 and December 31, 1967. Their

From the Department of Surgery, University of California School of Medicine, San Francisco.

Submitted 31 January 1969.

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ages ranged from 52 to 77 years with a mean age of 63 years. Thirteen of the patients (30 percent) were over 70 years of age.

Pathologic Characteristics. All aneurysms involved the infra-renal abdominal aorta. Variable degrees of enlargement in the common iliac arteries were also present. The site of rupture was the aorta in 42 patients and the common iliac artery in two. Five categories of rupture, depending upon the direction and extent, could be identified. Four patients had limited extravasation of blood beneath the adventitia of the aorta (sealed). In 23 patients rupture had extended through the adventitia into the retroperitoneum (contained). In 13 patients, rupture, usually from the anterior wall of the aneurysm, produced intra-peritoneal hemorrhage (free). The aneurysm ruptured into the duodenum in two patients and into the inferior vena cava in two.

The diameter of the aortic aneurysms varied from 7 cm to 17 cm (mean 11 cm). In the two patients with rupture of the iliac portion the diameter of the associated iliac aneurysm was 6 cm. (The average external diameter of the aorta and common iliac arteries is 3 cm and 1.5 cm respectively.)

Clinical Features. Except for massive gastroduodenal hemorrhage from aorto-duodenal fistula and acute intractable congestive failure secondary to rupture into the inferior vena cava, the clinical features in patients with ruptured aneurysms were remarkably consistent and typical. Abdominal or back pain and a pulsatile abdominal mass were uniformly present.² Twenty-six patients (59 percent) were in shock at the time of admission to hospital. The duration of acute symptoms before admission in the 32 patients who could give a reliable history ranged from six hours to 21 days; the average was three and a half days. Faintness or temporary loss of consciousness frequently appeared at the onset of pain. Over half of the patients had early improvement in both pain and light-headedness. Subsequent recurrence or increase of pain, hours or even days after onset, was accompanied by profound and persistent fall in blood pressure.

Two-thirds of the patients were asymptomatic before rupture occurred and were unaware that an aneurysm was present. Continuous abdominal pain lasting for more than a month before rupture of the aneurysm was the complaint leading to an ear-

TABLE 1.—Causes of Operative Mortality in Ruptured Abdominal Aneurysm

Postoperative Day		Cause of Death
Intraoperative (11 deaths)		Shock
Postoperative (11 deaths)	1	Myocardial infarction
	2	Graft thrombosis
	2	Gangrene of colon
	6	Hepatic and renal failure
	7	Aspiration pneumonia
	7	Renal artery thrombosis; renal failure
	8	Anastomotic leak with hemorrhage, occlusion of renal vein and renal failure
	8	Intestinal infarction, femoral artery occlusion, and renal failure
	10*	Myocardial infarction
	14	Pulmonary sepsis and renal failure
	30*	Pulmonary sepsis and pulmonary insufficiency

*No preoperative shock.

lier diagnosis in the 13 patients who were known to have an aneurysm before rupture occurred.

Management

All patients were taken immediately to the operating room. Only for patients without shock and with stable blood pressure was operation delayed to permit skin preparation, cross-matching and obtaining blood. In patients with shock, operation was begun after minimal skin preparation, and unmatched Type O blood was used. In these patients the average between hospital admittance and laparotomy was 50 minutes.

Proximal control of bleeding was obtained by cross-clamping the aorta above the aneurysm and below the renal arteries. This portion of the dissection, although often accomplished without direct vision, was usually facilitated by the dissection produced by the hematoma around the aorta. The remainder of the operation was performed in the usual manner for graft replacement of the abdominal aorta.

Results

Twenty-two (50 percent) of the 44 patients died during the time in hospital. Three others died subsequently from complications of operation. The causes of death are shown in Table 1. Although numerous causes are listed, at least one of three factors unique to the circumstance of aortic rup-

TABLE 2.—Incidence of Shock and Mortality in Various Types of Rupture of Abdominal Aneurysm

Type of Rupture	No. of Patients	No. of Patients In Shock	No. of Deaths Postoperatively	Mortality (Percent)
Sealed	4	0	0	0
Contained				
Small	7	1	1	14
Large	16	12	11	69
Free	13	11	9	69
Aorto-duodenal	2	2	1	50
Aorto-caval	2	0	0	0
Total	44	26	22	50

ture, and rarely encountered in elective aneurysmectomy, can be identified in each case. These common factors are shock, sepsis and iatrogenic injury.

Shock. Death as a result of prolonged shock resulted from failure of one or more organ systems (heart, kidneys, lungs and liver). Cardiac arrest following prolonged shock was the immediate cause of death in the 11 patients who died before leaving the operating room. Recent myocardial infarction was found at autopsy in five of these patients. Prolonged preoperative shock had been present in one of the two patients who died postoperatively from myocardial infarction. Renal failure, secondary to shock, was the cause of death in four patients who survived the immediate operation.

The vasodilatation that occurs with general anesthesia usually compounded the problem of blood pressure control. The blood pressure of those patients already in shock was further depressed. In a few patients whose blood pressures appeared to be controlled on arrival to the operating room, pressure dropped to shock levels once anesthesia was started.

The response to fluid replacement in the management of shock was the critical factor in survival. Twenty-six patients were in shock when they entered the hospital. In 21 of these patients shock was refractory to volume replacement and only two survived. Normal blood pressures were restored in five patients and three of them survived.

Sepsis. Local graft sepsis followed by anastomotic disruption led to death in three patients; two of them died six weeks postoperatively and one died nine months postoperatively. One patient had sepsis after the repair of the aortoduodenal fistula. In the second patient, one ureter had been transected and, although repaired, this was considered to be the cause of retroperitoneal infection. In the

third patient, in whom retroperitoneal abscess led to anastomotic disruption nine months postoperatively, operation had been performed without sterile preparation.

Iatrogenic Factors. Technical errors, which rarely occur during elective aneurysmal operations, were the result of the need for haste and the distortion and obscuration of the normal anatomy which the aortic rupture had caused. Laceration of an iliac vein in one patient, transection of a ureter in another and thrombosis of a renal artery in a third all contributed to a fatal outcome. In two patients, gangrene of the left colon was probably the result of ligature of the inferior mesenteric artery at a level more distal to that used in an elective operation.³

The deaths from graft thrombosis (one patient), pulmonary sepsis (one patient) and aspiration pneumonia (one patient) were the only ones not specifically related to rupture of the aneurysm.

Nineteen patients survived the operation without late complications. No follow-up information is available on one of these patients and two have died from unrelated disease. Sixteen patients were living and well without further arterial difficulties at the time this report was written.

Discussion

The lethal influence of shock and the problem of its control in patients with aortic rupture have long been recognized.^{1,4,5} In this series, when shock was overcome the mortality rate was 10 percent, but when shock was prolonged the mortality rate was 90 percent. A review of the case histories and the pathologic findings strongly suggests that most of the patients who died would have survived if the diagnosis had been made with the first onset of symptoms and operation had been performed immediately. Among the patients with various pathologic categories of rupture, those with sealed rupture and the most favorable prognosis were operated upon early. Those in prolonged shock, in whom bleeding had extended into the retroperitoneum and abdominal cavity, were generally operated upon late. The comparative mortality rates in these categories are given in Table 2.

These observations suggest that rupture often begins with self-limited extravasation into the sub-adventitia or peri-aortic tissue. Pain and a temporary systemic response to minor blood loss are experienced. A variable period of time may then elapse before rupture extends into the less resistant

area of the retroperitoneum.⁵ It is during this period, when the patient's blood pressure is stable and only a minor distortion of peri-aortic structures has occurred, that aneurysmectomy can be performed with a risk little greater than that in operation for unruptured aneurysms. Since the aneurysm can be expected to exceed 7 cm in diameter⁶ it should be readily detected by abdominal palpation. Even if the diagnosis of aortic rupture is wrong, nothing would be lost by early operation since the threat of eventual rupture is an indication for elective resection for aneurysms reaching this size.

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CLASSIFICATION OF EYE CHANGES IN GRAVES' DISEASE

"[In the new system for classifying or grading eye changes in Graves' disease approved by the American Thyroid Association], the plan is to have classes. Obviously, Class O means that nothing is wrong with the patient, even though he may be thyrotoxic. Class I is the category that used to be called mild or noninfiltrative, namely that end of the spectrum where eye changes are only cosmetic; and that means the signs are present, but none of the alarming symptoms — burning, tearing, sandiness, etc. To distinguish this, we made a separate category, even though proptosis is obviously common to both the more severe changes and this relatively mild area where the prognosis is excellent no matter what you do.

"Now from this point on we get involved with the serious kind of eye changes known in the past as the infiltrative or severe, where the patient often starts out with some tissue involvement and no proptosis, maybe nothing except a feeling of irritation. It's often called allergy by the ophthalmologist or it's mistaken for conjunctivitis or something of that sort. It isn't till later that the suspicion dawns that this is Graves' disease. You go from there to proptosis, which is a little bit more advanced and then to extraocular muscle involvement which is still more advanced. Finally the last two [classes] which are quite serious as far as sight goes — corneal involvement and then loss of vision, which means the optic nerve is getting involved.

"This system accounts for practically every symptom and sign and lends itself to a mnemonic. . . . The idea is that 'no' means no serious prognosis; 'specs' is the bad part. Going in order this is no involvement, only signs; then comes soft tissue [involvement], proptosis, extraocular muscle [involvement], cornea [involvement], and sight [loss]. With the help of this mnemonic, the system is really awfully easy to use."

—SIDNEY C. WERNER, M.D., New York City
Extracted from *Audio-Digest Ophthalmology*,
Vol. 6, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Endemic Coccidioidomycosis in Northern California

An Outbreak in the Capay Valley of Yolo County

JOHN C. LOOFBOUROW, M.D., DEMOSTHENES PAPPAGIANIS, M.D., AND
THOMAS Y. COOPER, M.D., *Davis*

■ *Endemicity of coccidioidomycosis in Yolo County, outside previously known endemic areas, was confirmed by occurrence of a small epidemic. Eleven cases of clinically apparent coccidioidomycosis occurred among a group of 23 archaeology students. Eight of the cases were confirmed serologically, and three by skin test conversion alone.*

The specific site of exposure was an ancient Indian burial ground on Cache Creek near Brooks in the Capay Valley approximately 40 miles northwest of Sacramento.

SINCE THE FIRST DESCRIPTIONS of coccidioidomycosis 77 years ago, northerly limits of the endemic areas have been identified to lie, in general, in the San Joaquin Valley of California. The northernmost autochthonous cases of coccidioidomycosis have been described near Livermore, California, in the northeastern portion of Alameda County.

Yolo County has been suspected as an area in which additional cases of coccidioidomycosis have been acquired,¹ but the precise location of ex-

posure within Yolo County in those cases recognized here could not exclude with certainty a previous exposure in the known endemic areas. We report herein an epidemic that occurred in the summer of 1968, which confirms the endemicity of Yolo County and pinpoints an area of exposure within the county.

Description of Epidemic

An archaeology group from the University of California at Davis explored an Indian burial site near Brooks, California, in the period 16 June 1968 through 26 July 1968. On 9 July, a student member of that class was seen with pleuritic pain, fever, malaise and cough, and was found to have middle lobe pneumonia. Coccidioidomycosis was

From the Cowell Student Health Service, University of California, Davis (Loofbourow and Cooper), and the Department of Medical Microbiology, University of California, Davis, School of Medicine, Davis (Pappagianis).

These studies were supported in part by the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, Office of the Surgeon General of the Army.

Submitted 21 February 1969.

Reprint requests to: Cowell Student Health Service, University of California, Davis 95616 (Dr. Loofbourow).

TABLE 1.—*Clinical Data, Archaeology Class Coccidioidomycosis, Cowell Student Health Center, Summer 1968*

Case	Age	Sex	Onset of Symptoms	X-ray	Coccidioidin Skin Tests				Serology			
					1:100		1:10		Date	Precipitins	Complement Fixation	
1	21	M	9 July	Pos.	12 July	3mm	18 July	40mm	18 July	Pos.	Negative	
									5 Aug.	Neg.	4+1:2,4+1:4,2+1:8,neg. 1:16	
2	21	F	12 July	Pos.	15 July	Neg.	17 July	15mm	16 July	Neg.	Negative	
									Sept.	Neg.	4+1:2,1+1:4,neg. 1:8	
3	28	M	12 July	Neg.	17 July	5mm			19 July	Neg.	Negative	
									16 Aug.	Neg.	Negative	
									27 Sept.	Neg.	4+1:2	
4	19	M	22 July	Neg.	17 July	Neg.	22 July	Neg.	3 Sept.	Neg.	4+1:4,1+1:8,neg. 1:16	
5	23	F	28 July	Pos.	17 July	Neg.	22 July	Neg.	19 July	Neg.	Negative	
					6 Aug.	5mm	6 Aug.	10mm	2 Aug.	Neg.	Negative	
									7 Aug.	Pos.	Negative	
6	20	F	2 Aug. (mild)	Neg.	16 July	10mm			19 July	Neg.	4+1:8,3+1:16,2+1:32	
									27 Sept.	Neg.	4+1:2,3+1:4,2+1:8,neg. 1:16	
7	21	F	1-5 July	Neg.	17 July	Neg.			16 July	Neg.	Negative	
					24 July	25mm			5 Oct.	Neg.	4+1:2,1+1:4,neg. 1:8	
8	22	F	30 Aug.	Neg.	9 Oct.	15mm			8 Oct.		Anticomplementary, positive by immuno diffusion	
9	20	F	20 Aug.	Neg.	17 July	Neg.	22 July	4mm	30 July	Neg.	Negative	
					23 Aug.	15mm			Aug.	Neg.	Negative	
10	19	M	5 July	Neg.	17 July	Neg.			17 July	Neg.	Negative	
					18 Oct.	10mm			18 Oct.	Neg.	Negative	
11	21	F	None	Neg.	17 July	Neg.	19 July	Neg.	19 July	Neg.	Anticomplementary	
					5 Aug.	18mm			5 Sept.	Neg.	Negative	
12	20	M	1 Aug.	Neg.	17 July	Neg.	22 July	Neg.	19 July	Neg.	Negative	
					5 Aug.	18mm			2 Aug.	Neg.	Negative	
13	21	F	None	Neg.	15 July	15mm			19 July	Neg.	Negative	
									20 Aug.	Neg.	Negative	
14	21	F	None	Neg.	19 July	15mm			19 July	Neg.	Negative	
									4 Sept.	Neg.	Negative	
15	21	M	None	Neg.	17 July	13mm			19 July	Neg.	Negative	
									30 Aug.	Neg.	Negative	
16	20	M	None	Neg.	17 July	Neg.			19 July	Neg.	Anticomplementary	
17	59	M	None	Neg.	16 July	Neg.	22 July	Neg.	16 July	Neg.	Negative	
					28 Aug.	Neg.			Sept.	Neg.	Negative	
18	29	M	None	Neg.	18 July	14mm			17 July	Neg.	Negative	
19	18	F	None	Neg.	17 July	Neg.	22 July	Neg.	22 July	Neg.	Negative	
									Sept.	Neg.	Negative	
20	21	F	None	Neg.	12 July	Neg.	22 July	Neg.				
21	19	M	None	Neg.	17 July	Neg.	22 July	Neg.	contaminated		Anticomplementary	
22	26	F	None	Neg.	17 July	Neg.	22 July	Neg.	17 July	Neg.	Negative	
					8 Oct.	Equiv.			7 Oct.	Neg.	Negative	
23		M										

suspected on the basis of clinical manifestations and positive skin test response to 1:10 coccidioidin. The entire archaeology group was then tested, first with 1:100 dilution coccidioidin; and those who did not react to 1:100 were retested with the 1:10 dilution. Surveillance was continued for the duration of the archaeology course and, where possible, continued by mail with cooperating physicians thereafter.

Results of the initial survey and follow-up are recorded in Table 1. There were eight reactors to coccidioidin at the outset; four were symptomatic, and they later had positive serologic response for coccidioidomycosis (Cases 1, 2, 3 and 6, Table 1).

Four of the original reactors remained asymptomatic

and serologically negative (Cases 13, 14, 15 and 18) and one student (Case 23) refused to be tested because he had lived in the San Joaquin Valley and stated he had had a previous infection. These latter five were considered not at risk.

Three persons were negative to 1:100 coccidioidin at the outset but did not return for the 1:10 test. Of these, one (Case 16) remained well throughout the observation period. One (Case 7) developed clinical disease, skin test conversion and seroconversion; and one (Case 10) later had skin test conversion and signs suggestive of disease.

Ten subjects were originally skin test negative to both 1:100 and 1:10 dilution of coccidioidin. Of these, two later developed clinical disease and

converted serologically (Cases 4 and 5); three developed strongly positive skin tests without demonstrated sero-conversion (Cases 9, 11, 12). The remaining five patients (Cases 17, 19, 20, 21, 22) showed no evidence of clinical or subclinical coccidioidomycosis.

An interesting additional case occurred in a student (Case 8) who visited the site and worked for one day, on 30 August 1968. She developed an illness in mid-September consisting of cough, pleuritic chest pain, chills and low grade fever. She recovered from the illness in about two weeks, then became aware of coccidioidomycosis through a friend and sought medical advice at the Student Health Service. A skin test carried out on 8 October was strongly positive and a single specimen of serum obtained on 8 October was found to have coccidioidal antibodies.

Soil samples were obtained from the surface and to a depth of four inches at the excavation site, but at this writing have not yielded *C. immitis* either in cultures or animals inoculated directly.

Reports of Cases

Case 1 (Table 1). A 21-year-old Caucasian man was first seen at the Student Health Center 9 July 1968 with a two-day history of cough, pleuritic pain in the right anterior region of the chest, fever, chills and malaise. He had had heavy exposure to dust in the above described archaeological effort since 19 June. An x-ray film showed segmental right middle lobe pneumonia. A skin test with 1:100 coccidioidin was read at 48 hours as equivocal (4 to 5 mm induration and very faint erythema). The patient's symptoms lessened decidedly by 11 July, but a repeat skin test with 1:10 coccidioidin resulted in a reaction 40 mm x 25 mm. On 18 July precipitins were detectable. On 5 August a serum specimen showed fixation of complement (4+ at 1:4 dilution) although precipitins had faded. The patient recovered uneventfully and by November 1968 was asymptomatic and an x-ray film showed the chest had cleared completely.

Case 2 (Table 1). A 21-year-old Caucasian woman was seen on 16 July with pleuritic pain of five days' duration which had been preceded by a sore throat occurring about one week earlier. Skin test (1:100 coccidioidin) was negative at this time but an x-ray film showed pneumonia in the superior segment of the left lower lobe and she was admitted to the hospital. A repeat coccidi-

oidin skin test with a 1:10 dilution on 17 July was positive with 14 mm x 15 mm of induration. This patient had a previous history of acute glomerulonephritis and with the current illness albuminuria and hematuria developed. These conditions cleared completely by 13 August 1968. Antistreptolysin O titer remained negative (less than 50 Todd units). Coccidioidal serology on 16 July was negative but when retested in early September a specimen of serum fixed complement (4+ at 1:4 dilution by overnight complement binding). At present there is a residual radiographic density in the area of the previous pneumonia, although the patient is in good health and under the care of her personal physician.

Case 5 (Table 1). A 20-year-old Caucasian woman was found to be skin test negative at the original survey, had a clear x-ray film of the chest, and on 19 July coccidioidal serology was negative. The patient finished her course of study on 26 July and went to the Sierra Nevada Mountains where her husband was employed for the summer. She had been provided with information about coccidioidomycosis and a letter of instruction to give to her physician in case of illness. She was asked to have serologic and skin tests repeated in August in any case. On 28 July pleuritic pain developed on the right side. She was seen by a physician in Jackson, California, where a "spot" was noted on an x-ray film of the chest. Penicillin was given but chills, cough, fever and more severe pleuritic pain and erythema nodosum developed. The patient returned to her home near Sacramento, California, and was seen there by her personal physician, who made a tentative diagnosis of coccidioidomycosis. Because it was felt necessary that she be isolated (incorrectly, in our opinion), and no private isolation room was available, she returned to the Student Health Center and was admitted on 5 August after an roentgenogram of the chest showed consolidation of the superior segment of the right lower lobe. Coccidioidin skin test (1:100 dilution) produced 5 mm of induration and erythema, while the 1:10 dilution yielded a 10 mm reaction. On 7 August precipitins were detected in the serum. Erythema nodosum present during the acute phase subsided after one week and the patient was released to the care of her personal physician. We have no follow-up to date.

Case 10 (Table 1). A 19-year-old Caucasian male student when originally skin tested on 16 July 1968 had no reaction to 1:100 coccidioidin.

TABLE 2.—Average Monthly and Seasonal Precipitation 1967-1968
at Various Stations in Yolo County*

Station	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	June	Season
Brooks	.01	.02	.19	.96	1.75	4.17	4.06	4.10	2.63	1.31	.60	.20	20.00
Clarksburg	.01	.01	.21	1.10	1.57	2.95	3.45	3.44	2.39	1.61	.53	.09	17.36
Davis		.01	.17	.76	1.37	3.41	3.29	3.25	2.14	.36	.57	.13	16.46
Dunnigan		.01	.26	1.17	1.55	3.34	3.13	3.11	2.12	.39	.55	.16	16.79
Guinda	.01	.03	.53	.79	1.82	3.23	6.42	3.72	3.25	.97	.59	.13	21.49
Knights Landing		.03	.17	.78	1.46	3.35	2.99	2.92	2.22	1.42	.54	.22	16.10

* U.S. Soil Conservation Office, Woodland, Calif.

TABLE 3.—Suspected Autochthonous *Coccidioidomycosis*
—A Review of Recorded Diagnosis of Four Yolo County
Hospitals, 1958-1968

Age	Sex	Possible Origin of Infection
45	M	Rumsey
50	F	Dixon or Winters
37	M	Davis
64	F	Winters
22	M	Davis
35	M	Dixon
61	M	Guinda

He was retested on 18 October with 1:100 coccidioidin and showed a 15 mm reaction. In the interim he had had a chronic rash lasting about one month (presumed to be caused by poison oak) which had been treated with steroids, but had subsequently become asymptomatic. Coccidioid serologic tests remained negative through 18 October 1968.

Characteristics of the Endemic Region

Known endemic areas,² like those of Maddy's Lower Sonoran Life Zone,³ are characterized by scant rainfall, hot dry summers, alkaline soil, mild winters and sparse flora. The Capay Valley of Yolo County (Figure 1) in Northern California, and the specific site near Brooks, California, have these general characteristics although the soil is neutral, of physical class 2S-3, a 3 percent clay loam.⁴ The elevation above sea level of the site is approximately 300 feet. Rainfall in this area is moderate, occurring mostly in winter and spring (Table 2). The general climatic and terrain conditions of this area exist in the foothills of the central Sacramento Valley as far north as Red Bluff, California. Reference to the "Life-zone" map of Grinnell⁵ indicates that the Capay Valley lies outside (west of) the Lower Sonoran Life Zone.

The excavation site lay on either side of a dirt road which parallels Cache Creek in its course through a small meadow. The flat meadow is irri-

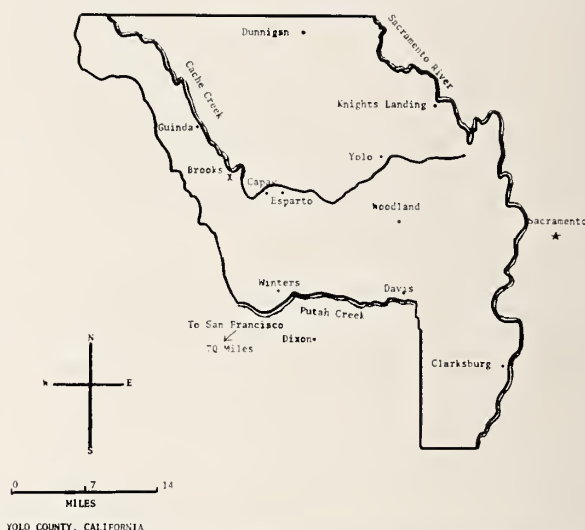


Figure 1.—Map of Yolo County with the approximate site of exposure (X) at Cache Creek near Brooks.

gated and farmed, the irrigation ditch running beside the road.

Discussion

The archaeological group described above concentrated its work during the academic Summer Session only at the above-described diggings, and there is little doubt that the reported cases of coccidioidomycosis were acquired at that site. With this demonstration, Yolo County can be added to the known endemic areas for coccidioidomycosis. The nearest previously demonstrated endemic area is the Livermore Valley, approximately 80 miles to the south. Several isolated cases of coccidioidomycosis in humans have been reported in Yolo County in the past. A ten-year review of coccidioidomycosis cases in four hospitals in Yolo County (1958-1968) reveals a number of cases which may have been autochthonous (Table 3). Heretofore, it has not been possible, however, to exclude the possibility that these infections resulted from visiting known endemic areas,

or from fomite transfer. For example, Pulford and Larson¹ described a fatal case of coccidioidomycosis in a male resident of Woodland. The apparent onset of his illness was in November 1926, although he had been to the San Joaquin Valley (Modesto) on three occasions in August 1926. An additional local case of coccidioidomycosis was recently proved in a simian subject kept out of doors in the Davis area for the past three to four years.⁶

The occupational considerations in this episode are noteworthy. Archaeology is one of the vocations which commonly involve exposure to dust. Other examples of such vocations are construction, surveying, agriculture, oil drilling, anthropology. In the present case soil was removed from the study site and screened in a rocker-type screen, which in dry conditions exposes the operators and those nearby to large amounts of dust. Outbreaks have occurred among archaeological and anthropological groups in endemic areas of California several times in recent years.^{7,8,9}

Among those measures which should be helpful in controlling exposures are the following: skin testing of persons who are to work in endemic areas; dust control measures; careful medical follow-up of exposed individuals; educational programs aimed at those in high risk occupational

groups as well as those professional or managerial people dealing with such groups. While no specific measure can be recommended it should be helpful to attempt to minimize exposure to dust.¹⁰

The increasing use of heavy equipment in construction and agriculture that exposes operators to dust, and increasing archaeological and anthropological interest in the North American Indian are likely to lead to other exposures and possibly to documentation of additional areas of endemicity. Awareness of this possibility by physicians should be helpful in early discovery of new cases, and their proper management.

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DRUG COMPLICATIONS OF ANEMIA IN PREGNANCY

"Anemia is a common factor — in fact, it's an occupational hazard — of the multigravida, especially in indigent populations. Iron deficiency and megaloblastic anemias do not respond as well, and in fact sometimes will not respond at all, to therapy when chloramphenicol (trade named Chloromycetin) has been used as a drug for treatment of infection. It is also thought, but not as clearly demonstrated in the literature, that tetracycline will do the same; and both of these drugs do inhibit protein synthesis."

—WILLIAM A. LITTLE, M.D., Miami

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The Mentally Retarded Infant

Is Placement Feasible?

ELLEN S. ALKON, M.D., M.P.H., AND RONALD L. THIELE, M.D., M.P.H., *Berkeley*

■ *A 1968 questionnaire about placement resources for mentally retarded infants that was sent to public agencies in all 58 California counties showed:*

- *Resources for counseling, placement, and financial aid for out-of-home placement are not uniformly available to all groups within the population.*

- *Financial help with out-of-home placement of a member of a family that is not medically indigent may be available in less than one-fourth of the counties of the state.*

- *Knowledge of resources is often inadequate. A family could be referred inappropriately from one agency to another.*

RETARDED INFANTS need both immediate and long-term continuing care. When such an infant is first identified, the family and the physician usually discuss plans to obtain this care. Although the majority of retarded infants can be cared for by their own family, some families are advised or may desire to seek immediate out-of-home placement. Other infants have special nursing and medical care needs, such as tube feeding or respiratory support, which may necessitate prolonged hospital care. Several steps should be taken before placement is recommended and before families make such a decision:

- Accurate diagnosis and determination of the infant's medical or nursing needs.

- Counseling with parents to help them cope with their feelings, appraise their capabilities of care, and determine if placement is desired.

- Location of appropriate resources to assist the family including short or long term financially feasible out-of-home placement, if this is desired.

The present study was undertaken to determine the availability of specific resources within public agencies in each California county to fulfill the needs of families for counseling and locating resources, including financially feasible out-of-home placement for mentally retarded infants.

In January 1968 a specially designed short questionnaire was sent to all California county welfare departments,¹ city and county health departments,² county probation departments,³ county general hospitals,⁴ and the state hospitals for the mentally retarded and their four outpatient units. Twenty-four persons, professional and lay, serving in an official coordinating and planning capacity for Mental Retardation in their county or region also were queried.

From the Division of Maternal and Child Health, University of California, School of Public Health, Berkeley.

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Reprint requests to: Division of Maternal and Child Health, University of California, School of Public Health, Berkeley 94720 (Dr. Alkon).

TABLE 1.—*Services for Mentally Retarded Infants Reported by California Public Agencies in 1967*

	Local Facilities				State Hospital Out-patient Units
	County General Hospital	Health Department	Welfare Department	Probation Department	
Agencies identified, and percent responding	51 (82%)	61 (100%)	58 (95%)	58 (93%)	4 (100%)
Agencies having serviced a family with a retarded infant	21	33	25	27	4
Agencies offering some kind of parent counseling	23	59	52	no answer	4
Agencies offering help locating community placement	21	20	45	35*	no answer

*35 respondents thought the court would be likely to order out-of-home placement for the infant if the court could gain jurisdiction.

TABLE 2.—*Admission Policies for Retarded Infants at 42 California County General Hospitals in 1967*

Infant's care needs	Admission Policies	
	Short term care only	Prolonged care
Needs special care	22	17
No special care needs	27*	6

*Five of these hospital accept infants with no special care needs only on court referral.

Results

Analysis of the questionnaire responses indicated that patterns of counseling services, location and arrangement for out-of-home placement and financial assistance for placement are unique to each county. Some of the responses are summarized in Table 1.

County General Hospitals

Twenty-one county general hospitals reported that they cared for a retarded infant in 1967, but these hospitals were not always among the 23 hospitals which could offer parent counseling, or the 21 hospitals which could help locate community placement. The usual service of the county hospital was interim placement with a usual duration of hospital care of less than one month, although prolonged care may be offered (see Table 2).

Each of the 39 hospitals who would admit a retarded infant, including the five hospitals which are restricted to the medically indigent, charge fees. Eighteen of the 39 hospitals charge everyone full fees, and ten of these 18 may require a property lien.

Health Departments

While 33 of the 61 local California health departments reported service for the family of a retarded infant in 1967, 59 offered parent counseling, and 20 could help locate community placement.

Welfare Departments

Although 52 of the 55 responding county welfare departments could counsel families with a retarded infant and 45 could help locate community placement, the families' financial status may determine who can receive service. Six of the departments could only provide these services for families on public assistance, and an additional three could provide service only if the family was on public assistance or medically indigent (eligible for Group II Medi-Cal). Seven welfare departments that offer counseling reported a serious limitation in this service, and many departments indicated a scarcity of adequate resources for community placement.

While 48 welfare departments reported that they could offer financial assistance for out-of-home placement of a retarded infant if his family was on public assistance, only six could offer financial assistance with placement to the family who did not qualify as medically indigent or eligible for public assistance.

Probation Departments

Homeless and mistreated children and retarded children whose families are found by the court to be unwilling or incapable of "exercising proper and effective parental care"⁵ can be made wards of the court, and hence a public responsibility.

Thirty-three county probation departments in California process applications to the state hospitals for the mentally retarded; in spite of this, only eight of these 33 replied that the placement of a retarded infant is a proper concern of the probation department. Thirty-five of the respondents thought their county court would likely order out-of-home placement if the parents were found to fit the above description, and an additional seven *might* order out-of-home placement. Although 13 counties reported that out-of-home placement was unlikely, some of these reported actually handling similar cases through out-of-home placement. Forty probation departments reported foster home placement. County hospitals and shelter care in detention facilities are also utilized.

State Hospitals for the Mentally Retarded

Four state hospitals in California provide nursery care for retarded infants. In 1967 admission to these hospitals was possible in less than three weeks for infants with special problems needing medical care in a hospital. Healthy retarded infants without special care needs, on the other hand, are not eligible for rapid admission. Thus no state hospital admitted healthy infants with Downs' syndrome during 1967, and patients with this condition were actually admitted at average ages from four to nine years.

Outpatient Units

Each of the four state hospitals for the retarded has an outpatient unit available to residents within its region. All offer family counseling although one of them is able to offer only short-term counseling. Two also offer physician consultation. All may offer pre-admission study, and may expedite the admission of the newborn with special care needs. The mother's inability to care for her infants, or the lack of community resources alone would not be sufficient reason for admission, according to two of the outpatient units.

Mental Retardation Coordinators

Of the 24 questionnaires sent to individuals in mental retardation planning and coordinating positions, 21 (88 percent) were returned. The respondents reported only those resources also mentioned by the public agencies. Many commented on the problem of inappropriate referrals and the lack of coordination of existing resources for the retarded.

Referrals

When a family does not meet the eligibility requirements of an agency or needs help other than what is offered, they should be appropriately referred. Of the respondents, 76 percent of the county hospitals, 87 percent of the health departments, 78 percent of the welfare departments and 51 percent of the probation departments reported where they referred these families.

Most of the reported referrals were from one public agency to another public agency. Welfare departments received referrals from 45 percent of the county hospitals, 41 percent of the health departments, and 36 percent of the probation departments which recorded referrals. The welfare departments, in turn, would make their referrals to health departments, probation departments, and one of the divisions of the Department of Mental Hygiene. Only 14 percent of all responding agencies would refer a family to a community mental health (Short-Doyle) program.

Although many referrals were appropriate for the service desired, many inappropriate ones were reported. For example, nine agencies mistakenly refer to Crippled Children's Services for help with out-of-home placement. Five agencies would refer to the probation department in counties where the court is unlikely to order out-of-home placement. Four agencies reported referring cases to the welfare department in counties where placement help is not offered by the welfare department. Six agencies mentioned a regional center for mental retardation in counties where no such center existed, and one mentioned referral for placement to a health department which does not offer placement assistance.

Some form of information and referral service for the mentally retarded was reported to exist in 30 (52 percent) of the California counties. However, utilization is obviously incomplete, for in five of these counties agencies disagreed about the existence of such a service.

Discussion

We recognize the following limitations in interpretation of the responses to the questionnaire: (1) Each questionnaire was filled out by one individual within an agency; this person may have interpreted the questions or his own agency policy differently from what might have been the interpretation by another individual in the same agency; (2) The questionnaire possibly may not have

elicited information on all community resources; (3) The answers given may reflect only the policy of the agency as stated by the individual respondent at that moment; (4) The questionnaire asked only for specific information on the existence, not the quality or adequacy of service. Nevertheless, we think that certain trends are apparent and that these are of importance to professionals who serve families with retarded children.

Initial identification of the retarded infant is generally made by the attending physician.⁶ Further evaluation may be available in one of the highly skilled diagnostic units which are accessible to some areas of the state. These evaluation services can provide an important resource for family counseling.

A recommendation for placement is likely to produce the desire for placement,⁷ regardless of the feasibility or suitability of such a step. All families, regardless of their social and financial status, need immediate counseling to help them with their feelings about their new retarded infant, to plan realistically and to implement these plans. The physician having the first contact with the family should initiate the counseling process.⁸ Helping a family emotionally before they reach a decision, and guiding them to realistic resources is a job which usually is best done by a counselor in collaboration with a physician. Our study indicated that resources for professional collaboration in this process, even if not uniform in every community, are sometimes available.

The decision to seek out-of-home placement of the infant may be reached by some families. At this point, further direction and assistance are needed in locating the resources to provide that care. If according to the state hospital an infant requires hospital care, admission to a state hospital is reportedly possible within a short time. If the infant is not eligible for a state hospital, then community placement is the only alternative.

County hospitals serve as a temporary resource in many areas. Although directories of approved placements are available, individual families are rarely equipped to judge the suitability of these homes for their infant. The availability of professional help with placement may be financially determined. Infant placement in some counties is not possible because of insufficient resources.

Financial Help

Even if placement seems appropriate for the

infant and the family, it may be financially impossible or economically destructive. The quoted cost for a placement usually does not include clothing, medical care, and incidental expenses. In 1965 the average annual cost of maintaining a retarded child in out-of-home community placement in Los Angeles was estimated to be in excess of \$2,000.⁹ This cost was based on a fee of \$105 to \$175 per month. The current cost is undoubtedly higher since the monthly fees in a nursery facility in 1967 in Los Angeles ranged from \$135 to in excess of \$285.¹⁰

Financial assistance with placement was reportedly available from welfare departments in 48 of 53 counties for families eligible for welfare, in 13 of 48 counties for families considered medically indigent, and only in six of 49 counties for families not medically indigent. For families to whom this assistance is not available, several other resources may be considered:

- Private foundations sometimes offer temporary help.
- Probation departments do assume responsibility for some infants if the family undergoes the ordeal of having itself found unwilling to exercise care of the infant.
- Regional centers, in the counties they serve, within the limits of staff time, participate financially in a program that meets the particular needs of the individual.
- The Bureau of Social Work, California Department of Social Welfare, can place a limited number of retarded children in the community as an alternative to state hospital placement.
- Armed forces personnel dependents have financial aid available to them for out-of-home placement from the military dependents medical care program.

Despite these resources, out-of-home placement will be impossible for many families because financial assistance is not available to them. Only 14 (24 percent) of the counties reported some mechanism other than probation to help pay for out-of-home placement when the family is not medically indigent.

Unless emotional, situational and financial help are available, it may be impossible to implement a recommendation for out-of-home placement of a healthy retarded newborn. If a family receives this recommendation but can not place the infant, their iatrogenic desire to have the infant out of their home may produce unnecessary misery.

Therefore, a physician helping a family plan for the care of a retarded infant should be aware both of the need for counseling to help the family reach a suitable plan and the real limits which are posed by the scarcity and expense of suitable community placement.

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PSYCHIATRIC REFERRAL FOR TEEN-AGER DRUG USERS

What are your indications for referring a teen-ager who is a drug user to a psychiatrist?

"I think that one of the main danger signs in dealing with adolescents is depression; which is, after all, sometimes the precursor to suicide. . . . In talking with young people, I think one should gauge the depth of the depression carefully and face up to the issue of suicide. . . . These young people aren't afraid to talk about suicide. Some of them enjoy talking about it, and these are probably the ones that you need to worry less about. The ones who express real worry about what they may do to themselves and who are contemplating some particular method of committing suicide certainly should be referred immediately for some kind of psychiatric help.

"[Two other considerations are important in thinking about referral.] One is if you feel that you're not communicating with your patient—that you don't understand what he is saying, or you're on another wave length, or somehow you're not meeting—this is a reason to refer. It may just be that he doesn't like you very much; but it may also mean that he feels unhappy because he hasn't made contact, and this may make him more frustrated and more desperate. The other thing, which is a clue, is your own anxiety level. If you're talking with a patient, and for some reason he makes you very nervous and upset and scared and you start dreaming about him at night, this is a good reason to get somebody else to see him and size up the situation."

—GRAHAM B. BLAINE, JR., M.D., Boston
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The Blood Bank as a Public Health Service

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WILLIAM H. ADASHEK, M.D., *Los Angeles*

■ *The donation of blood is presented to the public as an altruistic service in which one human helps another. At the same time, the donor receives some help for himself. In the process of blood donation, a medical history is taken, an extremely short physical examination is done, and the donor's blood is studied by various tests. Although this is by no means the equivalent of a complete physical examination performed by a physician, it sometimes can be helpful in discovering early disease or other medical findings which could be pertinent to the donor's health.*

ALMOST ALL practitioners of medicine look upon the community blood bank as providing a needed local service. Patients who could not have survived in previous years are now living because of the easy availability of blood and blood products. Thus, we can truthfully tell donors that they are performing a great humanitarian service since their blood will help someone. At the same time, a donor may benefit beyond the feeling of altruism, for in the process of giving blood he will be subjected to a moderate medical scanning during which some forms of disease may be discovered in their earlier stages. Although by no means the equivalent of a complete history and physical examination performed by his own physician, the cursory examination of a donor has been designed

to demonstrate some major disease categories. For many persons who refuse to have or procrastinate in having a routine physical examination, it is better than nothing. This public health function of blood banking has recently been the subject of editorial comment.¹

What happens medically to a donor when he decides to give blood? First, a medical history is taken. Certain questions in this history are designed to elicit information on conditions that might make donating blood inimical to the donor's health. Others pertain to several disease states which might prove harmful to the recipient. A sample set of questions is shown in Table 1. All answers suggestive of disease are evaluated by the attending physician to see if they are truly significant. In addition, a history of symptoms such as productive cough, chest pain or convulsions is analyzed by the attending physician. If any appear significant the donor is rejected.

During the history taking, a certain amount of donor education takes place. Many of our prospective donors do not know that a carrier state

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Submitted 27 November 1968.

Reprint requests to: Scientific Director, Los Angeles-Orange Counties Red Cross Blood Center, 1150 So. Vermont Avenue, Los Angeles 90006 (Dr. Myhre).

	<i>To Protect Donor</i>	<i>To Protect Recipient</i>	<i>To Protect Both</i>
	Weight	Blood Transfusion within 6 months	Surgical oper. within 6 months
	Pulse	Malaria within 2 years	Fever
	Blood Pressure	Undulant fever	Polycythemia
	Hemoglobin	Eczema, dermatitis	Asthma
	Illness, last month	Immunization	Diabetes
	Rheumatic Fever	Hepatitis or jaundice	Tuberculosis
	Heart Trouble	Contact: Inf. Hepatitis	Cancer
	Pain in Chest	Allergy, hives	Under M.D.'s care
	Short of Breath	Arms examined (needle marks & infections)	Pregnancy within 1 year
	Fainting Spells	Infectious mononucleosis	
	Convulsions	Tattoo within 6 months	
	Hazardous occupation		
	When last donation?		

TABLE 2.—*Analysis of Persons Rejected for Blood Donation — One Year's Experience*

<i>Reason for Rejection</i>	<i>Percent of Total Rejects</i>
Low Hemoglobin Level	56.0
Blood Pressure	6.6
Hypertensive (6.2%)	
Hypotensive (0.4%)	
Illness during past month	8.1
Elevated Temperature	1.5
Irregular or rapid pulse	1.5
Cardiac or Vascular Disease	1.9
Pain in Chest	0.15
Shortness of Breath	0.07
Persistent Cough	0.09
History of Tuberculosis	0.12
Surgery within past six months	1.51
Blood Transfusion within 6 mos.	0.19
Dizziness or Fainting Spells	0.48
Convulsions	0.17
Epilepsy	0.16
Near Faint at Hemoglobin Table	0.62
Pregnancy within one year	2.86
Immunizations or Injections	1.9
Exposure to Contagious Disease	0.21
Hepatitis within 2 years*	1.1
Hepatitis contact (6 months)	0.8
Polycythemia	0.23
Diabetes	0.32
Rheumatic Fever	0.25
Brucellosis or Prolonged Fever	0.39
Malaria or Suppressant Drugs	0.16
Malignancy	0.15
Infectious Mononucleosis	0.23
Venereal Disease (information volunteered by Donor)	0.09
Hay Fever or Allergy	0.47
Asthma	0.25
Dermatitis, Eczema, Boils	0.6
Tooth Extraction (within 10 days)	2.18
Nervous/did not feel well	0.18
Under Doctor's Care/Misc. Medical	2.76
Miscellaneous Non-Medical	5.62

*Since our center no longer accepts blood from such donors for plasma fractionation, it is estimated that this figure will be about 6 percent.

exists in certain diseases such as hepatitis or other blood-borne diseases. Our statistics show that roughly 400 persons (0.2 percent) presenting themselves for blood donation are rejected yearly because of having had hepatitis or having been exposed to the disease; and 10.7 percent of all who

offer blood are rejected for some medical reason other than hepatitis. Results of a one-year study of all donor rejections are given in Table 2.

During the physical examination, the donor's temperature is recorded, his pulse rate determined and his blood pressure measured. Significant deviations in body temperature are studied further. Occasionally the pulse rate determination permits the discovery of tachycardia or atrial fibrillation previously not known to the patient, and such patients are referred for medical study. A low pulse rate can present more of a problem. Many of the donors with this complaint are athletes, who may be accepted; but occasionally heart blocks can be discovered. About 0.7 percent of all persons presenting themselves for donation are rejected because of hypertension (systolic pressure more than 200 mm of mercury, diastolic—more than 100 mm). Such persons are sent to their physicians for further study. A few donors are found to be hypotensive and are rejected because of the high incidence of donor reactions associated with this abnormality. They too are asked to consult a physician.

One of the most important tests is the determination of the hemoglobin level. The copper sulfate specific gravity method is accepted by the National Institutes of Health and the California State Department of Public Health for mass screening of blood donors. There is a small factor of false-positive error, but the test does not pass an anemic person. Although other more accurate tests have been studied as a substitute,² the speed, low cost and ease of reading make the copper sulfate test a good one. Kliman³ has proposed using the microhematocrit to check all donors who fail the specific gravity test.

After the Donation

After the blood donation has been made, the diagnostic procedures are still not exhausted.

Every unit of blood is examined visually during labeling and again each time it is transferred to another hospital. This examination includes inspection of the red cell mass, the buffy coat and the color of the plasma. All units not visually acceptable are studied further and usually discarded. At the Los Angeles-Orange Counties Red Cross Blood Centers in the last two years, observation of a thick buffy coat led to diagnosis of three previously unknown cases of chronic myelogenous leukemia and one case of macroglobulinemia of Waldenström in apparently healthy donors. Blood units with very fatty plasma are also discarded. Most of the donors with fatty plasma are found to have no disease, but occasionally familial hyperlipemia or hypercholesterolemia may be discovered. Donors with obviously icteric plasma are advised to have jaundice studies performed and the blood from such donors is discarded.

There should be more frequent studies of the red cells but at this time there are few mass production methods. In one recent case, diagnosis of congenital elliptocytosis in the donor was made because the major crossmatch showed oval cells when examined microscopically. Today, with all the automated techniques available, there is no reason a complete blood study could not be performed on every donor if it were felt desirable by the medical community. Thus far it is not being done in most blood banks.

In the laboratory the blood is grouped for the ABO agglutinins and typed for Rh factors. Naturally occurring isoagglutinins (anti A and B) are determined and the results compared with red cell grouping. This comparison can also give an insight into the donor's health. Protein abnormalities such as are found in dysgammaglobulinemia, multiple myeloma, leukemia, liver disease and many others may be discovered by the failure of the red cell grouping to agree with the isoagglutinin confirmation.⁴ Further, some rare blood group antigens and antibodies may be found by this same apparent lack of agreement. All disagreements between red cell typing and serum confirmation should be studied to see if they are caused by disease in the donor.

Determination of the strength of the isoagglutinins which is needed to provide low titer blood may sometimes indicate a change in donor population. A recent study of the military personnel at Fort Knox⁵ has shown a decrease in the number

of low titer donors proportional to the increase in the number of donors immunized against plague.

In addition to providing the normal results for grouping, if the donor's cells are used as a control they will occasionally show an autoagglutinin which may be sequela of a mycoplasma infection or a precursor to an autoimmune hemolytic anemia or be due to other reasons, such as drug ingestion,⁶ all of which need to be studied. Some donors do have a positive Coombs test reaction with no apparent disease.⁷

Serological Tests for Syphilis

All donor bloods must be studied with a serological test for syphilis (STS). This is done in California by the Venereal Disease Research Laboratory (VDRL) method. At our blood center, where we have only voluntary donors, we encounter about 0.185 percent reactive or weakly reactive serological tests each year. If results are reactive, the donor is referred to his personal physician or to the Social Hygiene Clinic. It is relatively uncommon to discover a previously unknown case of syphilis; almost all donors with positive reaction have known of their infection. Some observers even feel that routine STS is of little value in the older age group⁸ and some believe that seropositive blood can be transfused safely if adequately quarantined.⁹ The studies of McGehee-Harvey,^{10,11} showed that in a high rate of patients with a biological false positive reaction some type of autoimmune disorder develops later in life. Hence this is probably as good a reason as any for performing the test. More hazardous is the donor with syphilis who has only recently been infected and is seronegative but has spirochetemia. In a documented case recently reported by Chambers,¹² a recipient was apparently infected by a platelet concentrate. Storage of blood for 96 hours at 4°C will kill the spirochetes and this danger can be eliminated. This is probably one good reason why use of fresh blood should be contraindicated except in an emergency. The danger, of course, exists also in fresh blood components.

In addition to grouping red cells for the usual ABO and Rh groups and types, our blood center, like many others conducts routine screening tests for rare blood groups. By this means we are able to develop a rare donor file which is of great value when rare blood is needed for a patient. In addition, the donor with a rare type, and his physician, will know of this fact. This knowledge may be of

great medical importance if the donor ever needs a blood transfusion.

Most blood banks are now screening all units for the presence of irregular antibodies. In fact since the beginning of 1968 this procedure has been required procedure in all Red Cross blood centers and is strongly urged by the American Association of Blood Banks. By the use of this method, the minor crossmatch may be eliminated,¹³ thus simplifying the hospital crossmatching procedure. The antibody screening also has an important function for the donor. Each donor with an unidentified antibody represents a potential crossmatching problem if he ever needs blood as a patient. If this is an uncommon antibody which requires time to identify, it can endanger his life. Most donors with antibodies have either been pregnant or have received prior blood transfusions¹⁴; therefore their history might cause one to suspect they could have an antibody, yet there are enough of those donors who have neither a history of pregnancy nor of having received blood transfusions and still have "naturally occurring antibodies" to pose a serious problem. Screening for and identification of these antibodies with subsequent notification of the donor prevents a sudden confrontation by this type of problem. Approximately 0.5 percent to 1 percent of donors in several studies were found to have irregular blood group antibodies.^{14,15,16}

It should be possible with the development of automation to perform not only blood grouping and antibody screening but also hematological and

chemical studies on all donor blood in the near future; indeed this has already been done in the case of hyperglycemia.¹⁷ By this means many borderline medical problems might be discovered. It is probable there will be more of this kind of investigation in the near future.

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"TUBE OSTOMY" TO AVOID NASAL INTUBATION

"I hate to think of myself lying in a hospital bed for a period of time [after colonic or rectal surgery] with a tube down my nose. So I do an awful lot of 'tube ostomies.' I put in just a couple of purse strings [sutures]; and then . . . I make sure that I get the tube through a little piece of omentum some place or through some fatty mesentery or something some place. I also make the tract as long as possible; and I don't sew the stomach against the peritoneum. There's not going to be any leakage if there's a little omentum there. But I make the tract a long one, and it won't stay open. The length of the tract, I think, is tremendously important."

—WILLIAM C. BECK, M.D., Philadelphia

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CASE REPORTS

Foreign Bodies in the Gastrointestinal Tract

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THE ABILITY OF THE stomach and intestines to function normally despite the presence of large quantities of potentially harmful objects such as pins, sticks and nails attests the remarkable durability of these organs. It also creates a diagnostic problem for the physician, for unless he has the evidence of roentgen films of the abdomen, he may remain ignorant of several pounds of foreign bodies (Figure 1) in a patient's stomach. This is particularly true of mentally retarded and psychotic patients who may be unable or unwilling to inform the physician of what they have done or of their symptoms.

The following three case histories illustrate some of the diagnostic and therapeutic problems encountered.

Case 1. A mentally retarded, hyperactive 18-year-old girl was admitted to the surgical ward with fever, elevated leukocyte count and a tender, non-movable mass in the lower right quadrant of the abdomen. Appendiceal abscess was the clinical diagnosis but at operation a large steel spike 7

inches long was found, its head in the cecum and the shaft embedded in indurated edematous tissues of the abdominal wall. The spike was removed and the cecal opening was closed.

A roentgenogram showed another nail and assorted other metallic and opaque foreign bodies in the upper abdomen.

On laparotomy the stomach was found to be packed to its limit with foreign materials. These included: a large sized, matching pair of socks, a coin purse, many large pieces of wood, a large nail, three open, bent safety pins, a roll of 1-inch adhe-



Figure 1.—(Case 2) Supine and roentgen film of the abdomen showing stomach filled with radio-opaque foreign bodies and situated in the right upper abdomen and right pelvis.

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Reprint requests to: 1759 North Orange Grove Ave., Pomona 91767.



Figure 2.—Some of the foreign bodies removed from stomach of patient in Case 1.

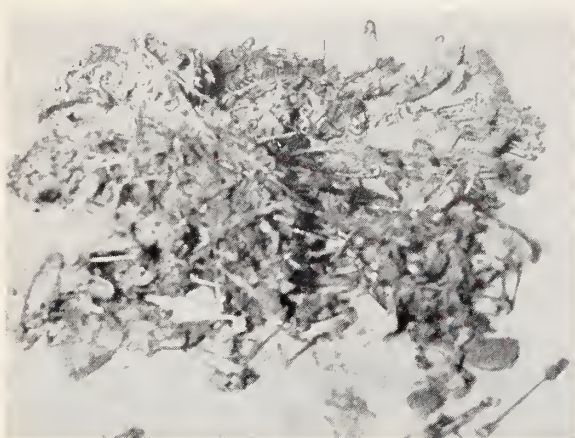


Figure 3.—(Case 2) Hundreds of safety pins and other hard objects tightly entwined in numerous threads, rags and strings removed at operation. See x-ray film (Figure 1).

sive tape, many pieces of rag and a considerable amount of thread, string and mattress stuffing (Figure 2). The weight of the stomach contents was 3½ pounds.

Up to the time of the symptoms that led to operation this patient's appetite was excellent and her nutritional status and hydration normal. There had been no loss or gain in weight in the preceding six months. It was not until the large spike had traversed the entire length of the small intestine and perforated the cecum, that illness occurred.

Case 2. The patient, a mongoloid woman 21 years of age, was referred to the surgical service after a physician, on routine periodic examination, noted a large, hard, nodular mass in the right upper abdomen that shifted to the pelvis when the patient sat erect or stood. There was no evidence of malnutrition or dehydration and no nausea, vomiting or loss of appetite. In fact, a preoperative note by a



Figure 4.—(Case 2) Film of abdomen several months after operation, showing open and closed safety pins, buttons, washers and gown fasteners in the gastrointestinal tract.

ward attendant stated that the patient had an excellent appetite and had gained 5 pounds in the preceding three months. Figure 1 is a preoperative roentgenogram of the abdomen.

On laparotomy the stomach was found to be filled to capacity with a hard, nodular mass. The stomach lay beneath the right lobe of the liver and the esophageal and duodenal attachments were twisted nearly 180 degrees. The stomach was opened and the mass was observed to be made up of hundreds of safety pins entwined in and fastened tightly together by numerous threads, rags and strings. For removal this conglomeration had to be cut into smaller pieces, which were then extracted with a sponge forceps. Total weight of the mass was 5 pounds, 13 ounces. It contained 757 large safety pins (691 closed, 21 open and 45 broken), 32 buttons, six rocks, one nail, one bobby pin, one zipper, one cherry pit, one tooth of a comb, one piece of wire, six strips of adhesive tape, six strips of canvas, and large masses of strings, threads, gown ties and twigs (Figure 3).

Postoperative recovery was uneventful. Roentgenographic examinations were carried out periodically afterward and additional safety pins, screws,



Figure 5. — (Case 3) Roentgen film of the abdomen showing numerous radio-opaque foreign bodies, also gas and fluid levels in the small intestine indicative of partial obstruction.



Figure 6. — (Case 3) Plain film of abdomen showing multiple small stones and gravel and a wire paper clip. Loops of small intestine greatly distended.

bolts and buttons were visualized (Figure 4). They were all either passed spontaneously or removed digitally from the rectum.

Case 3. The patient, a severely mentally retarded 16-year-old boy, had had abdominal laparotomy on five occasions to relieve intestinal obstruction caused by impaction of foreign materials.

An x-ray film of the abdomen (Figure 5) on the occasion of the first obstruction in 1961 showed multiple small radio-opaque foreign bodies scattered throughout the gastrointestinal tract — two closed safety pins, several washers, a lock-nut, two bicycle chain links and a thumb tack. Also noted were gas and fluid levels indicating partial intestinal obstruction.

Another roentgenogram, obtained before operation in 1962, showed numerous opaque foreign bodies and gaseous intestinal distention (Figure 6). At laparotomy the ileum was found to be greatly distended, owing to a large mass 7 inches proximal to the cecum that was completely occluding the ileal lumen. The obstructing foreign bodies were a large sheet of plastic mattress cover, strips of blue denim, a picture hook, two matches, celluloid tags, metallic buttons and a safety pin.

Throughout 1963 this patient continued to ingest foreign bodies. Nurses reported removal of sticks, pins and linoleum from the patient's mouth, and the defecation of wood, tinfoil, strings, leaves, rags, thumbtacks and a zipper.

In 1964 the patient returned for surgical care of still another intestinal obstruction. On abdominal exploration a segment of mid-ileum was found to be distended with gas, fluid and foreign bodies. Enterostomy was carried out and a closed safety pin, two shoelaces, many pieces of cloth and string, and two large pieces of mattress cover were removed. At a second site of obstruction 3 feet proximal to the first, additional impacted mattress cover and rags were found.

Three additional abdominal operations for intestinal obstruction due to ingestion of foreign materials were performed on this patient, in 1964, 1965 and 1968. Pieces of plastic mattress cover measuring 16 x 6 cm, 13 x 5 cm, and 20 x 7 cm were removed from sites of obstruction in the small intestine. On at least one occasion, an intestinal perforation at the site of a foreign body impaction required resection of the involved segment of small intestine. However, the patient's tolerance to ab-

dominal surgery is tremendous and he remained in excellent health despite continued ingestion of foreign materials and repeated operation.

Discussion

In the patients here reported upon, preventing ingestion of foreign bodies would entail either incarceration nude in an empty room or forceful restraint with a "straitjacket" of camisole type. We now advise annual abdominal roentgenograms on retarded patients in whom there is an increased likelihood of foreign body ingestion. More, identification beforehand of a "high risk" group will serve to focus attention on patients in whom prompt surgical intervention might be necessary should obstruction or perforation result.

A technique of "operant conditioning" was tried by the department of psychology in an unsuccessful attempt to train the patient in Case 3. An electric belt with mild shock device was used, but for only an hour each week. The patient soon learned not to ingest foreign bodies while the psychologist and apparatus were at hand, but his "appetite" for foreign bodies remained voracious in their absence. This technique of operant conditioning might well be effective if used by the nurses 24 hours a day for a long enough time.

Unlike Teimourian and coworkers,¹ who were dealing with psychotic patients, in the mentally retarded we have not found a high mortality rate associated with ingestion of foreign bodies. Over a ten-year period at least 20 patients have been treated at the Pacific State Hospital for gastrointestinal foreign bodies, several of them on more than one occasion. During that time there was only one death due to foreign bodies in the gastrointestinal tract, and it may well have been preventable, as it was associated with peritonitis resulting from tearing at the site of sutured junction of the sigmoid colon to the peritoneum in a colostomy.

The great majority of ingested foreign bodies, even those which are sharp and irregular and seem likely to cause perforation, usually pass spontaneously through the gastrointestinal tract with but minimal signs and symptoms. In the series of 20 patients observed in a ten-year period there were eight instances of open safety pins, from one to six in number, that passed through the entire gastrointestinal tract without causing perforation. The use of a high fiber diet, non-absorbable antibiotics or sulfonamides, and abundant patience, reinforced by frequent roentgenograms of the chest and abdo-

men and frequent clinical examinations, are usually adequate. However, when signs of intestinal obstruction, or particularly of perforation, do appear, prompt surgical intervention is mandatory.

Summary

Eight operative procedures were done on three mentally retarded patients for removal of ingested foreign bodies from the gastrointestinal tract. It was observed that the stomach, even when stuffed to capacity with foreign materials, could apparently function in a normal fashion. "Operant conditioning" using an electric belt with mild shock as a means to prevent ingestion of foreign bodies was tried in one case, but with only fleeting success, possibly because not continued long enough.

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Lymphangioma of the Pancreas With Symptoms of "Acute Surgical Abdomen"

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THE DIFFERENTIAL DIAGNOSIS when a patient has acute symptoms referable to the abdomen—"acute surgical abdomen"—includes an unending list of diseases involving almost every organ within or even adjacent to the abdominal area. That lymphangiomas may originate in virtually any organ system of the body (with the possible exception of the eye) is well recognized. The discovery of this lesion in the pancreas, though rare, is not unknown.^{1,2} The purpose of this report is to describe a case of acute hemorrhage into a lymphangioma of the pancreas in which the signs and symptoms were those of acute surgical abdomen.

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Reprint requests to: Department of Surgery, Childrens Hospital of Los Angeles, 4650 Sunset Boulevard, Los Angeles 90027 (Dr. Karlan).



Figure 1.—Film of abdomen with barium enema, showing large left upper quadrant mass displacing the splenic flexure inferiorly.

A 6½-year-old Negro girl was seen in the emergency room in August 1968 with complaint of stomachache of 24 hours' duration. She had been playing the previous afternoon, had eaten dinner, and in the early evening began to complain of a generalized abdominal ache. There was no known history of abdominal trauma although it was noted that the complaints began after she returned from the playground where she had been playing. She had intermittent nausea, with emesis on one occasion, and a low grade fever. She had been brought to the emergency room mainly because of the persistent abdominal pain. There was no history of any significant or similar illness in this child's past.

On physical examination, she was noted to have significant generalized abdominal tenderness without distention or rigidity and there was no rebound tenderness. Leukocytes numbered 16,700 per cu mm with a strong left shift in the differential. In the 12 hours after admission it became obvious that the tenderness was localized to the left upper quadrant, with minimal tenderness in the other quadrants. An intravenous pyelogram, barium

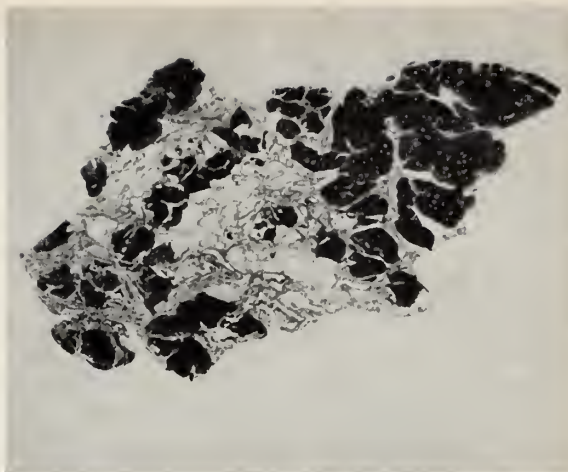


Figure 2.—Section of pancreas, showing diffuse lymphangioma (X5).

enema and upper gastrointestinal series all showed the presence of an extrinsic mass in the left upper quadrant which displaced the left transverse colon and splenic flexure downward (Figure 1), the left mid-ureter slightly medially and the proximal duodenum anteriorly. Serum amylase, electrolytes and blood urea nitrogen were within normal limits.

Exploratory laparotomy was performed approximately 18 hours after admission because of persistent pronounced localized left upper quadrant tenderness as well as the already mentioned laboratory findings. The preoperative diagnosis was "possible twisted mesenteric cyst." With the patient under anesthesia, a 7 to 8 cm mass was easily palpable in the left upper quadrant. The lesion was not visible until the lesser sac was opened and a multiloculated cystic mass was noted to be originating from the tail of the pancreas. The tumor measured 8 x 9 x 4 cm and weighed 160 grams. It consisted of many confluent cysts, each 2 to 3 cm in diameter and containing, for the most part, a clear yellow fluid. One larger cyst, measuring approximately 6 cm, was also present. It was filled with bloody fluid. Frozen section of the mass was reported as a possible benign cystadenoma of the pancreas (Figure 2). The pancreatic tissue adjacent and intertwining with the lymphangioma was normal both grossly and microscopically with no evidence of pancreatitis or other pathological process.

A distal one-third pancreatectomy and splenectomy were performed. The postoperative course was uneventful. A Chaffin tube draining the left subdiaphragmatic space was removed on the second postoperative day, as was a nasogastric tube

that had been placed for decompression. Ingestion of clear liquids was started on the sixth postoperative day and on the eleventh day the patient was discharged on a regular diet. Serum amylase during the postoperative period remained normal. When last seen several months later the patient continued to do well and had no residual effects.

Pathophysiology

Retroperitoneal lymphangiomas are exceedingly rare and especially unusual is one which arises from the tail of the pancreas. The majority opinion among investigators is that these lesions arise from congenitally misplaced lymphatic tissues.^{3,4,5,6} According to Sabin, the lymphatic system arises from the formation of five primary or primitive lymphatic sacs. It is believed that lymphangiomas developed during embryonic life from sequestered portions of these primary or primitive sacs. Secondary lymphatic structures developed after the primary sacs; these are the cisterna chyli, the thoracic duct and the subclavian sacs. Out-buddings from the five primary sacs propagate centrifugally to form the peripheral lymphatic system.

In the course of development of the lymphangectic channels, communications with venous systems normally develop. Failure to do so results in the enlargement of the space; thus cyst formation follows and the cysts enlarge. Hence the growth of a tumor. Theoretically then, a lymphangioma can form because of an obstruction of an existing lymphatic venous communication with proximal lymphatic dilatation or can arise from misplaced lymphatic tissue which fails to develop a vascular communication. Thus, it is not difficult to understand the presence of this lesion almost anywhere in the body.

Although symptoms are variable, these lesions are most often asymptomatic unless the mass stretches innervated structures to produce symptoms.⁷

In the case here reported, we have assumed that hemorrhage into one or more of the cysts brought about significant distention of the lesser sac area and its contiguous structures, causing pain. The cause of the hemorrhage is unknown, although minor trauma to the already present cystic enlargement could be postulated.

Discussion

This case represented a complex diagnostic and therapeutic challenge for the surgical staff. Partial pancreatectomy and splenectomy were recommended for complete removal of the tumor, since at the time of operation doubt existed as to the tissue type of the lesion. The preferred method of handling lymphangiomas is total excision without compromising adjacent vital structures. The complications of pancreatic operations can be alarmingly high (Warren) if certain safeguards are not followed during the resection. A clean, complete dissection across the pancreas in healthy tissue is necessary to avoid fistula, pseudocyst formation, recurrent tumor, recurrent pancreatitis or abscess formation.

In the present case the end of the pancreatic stump was ligated with non-absorbable silk sutures and the open duct was carefully closed. Chaffin tube drainage was maintained for 48 hours to approximate adjacent visceral tissue against the pancreatic stump and, last, Penrose drainage was placed to ensure protection should a fistula develop. There was no alteration in exocrine or endocrine pancreatic function in the postoperative period.

Summary

In a case report of lymphangioma of the pancreas, appearing as "acute surgical abdomen," partial pancreatectomy and splenectomy were carried out to eradicate the lesion completely, for the tissue type could not be determined immediately.

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Portal Hypertension—Current Status

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ABNORMAL ELEVATION of pressure within the portal venous system is of concern to the clinician because of the disabling complications which it presages and the considerable difficulties in the management of them. Esophageal or gastric varices, which develop in response to portal hypertension, are likely to bleed massively, an event of life-threatening proportions to the patient and one capable of severely taxing the resources both of physicians and of medical institutions. Similarly, the progressive accumulation of ascitic fluid brought about by obstruction to the egress of blood from the liver and also associated with portal hypertension, if unchecked, may lead the sufferer more slowly, but inexorably, to a death of inanition.

Disorders of liver function frequently precede the complications of portal hypertension and are intensified by them. Thus, the successful management of the patient with acute variceal hemorrhage, for example, may be severely hampered by abnormalities of ammonia metabolism, protein synthesis, detoxification systems, and glucose, salt, and water metabolism. Moreover, definitive treatment of portal hypertension by portosystemic shunt operations does little, of itself, to halt declining liver function.

As a result of the challenges implicit in these observations, much clinical and laboratory investigation has been directed toward portal hypertension in recent years. Despite new knowledge, many aspects of the pathophysiology and treatment of

portal hypertension remain controversial. The following report sets forth our views on the subject in the light of current information.

Etiology

Although many factors may contribute to the development of portal hypertension, central to our understanding of the pathophysiology of this disorder is the observation of an impediment to blood flow through the portal system. The schemes used to classify portal hypertension are based upon the anatomical location within the circulation where this increased resistance is believed to be produced. It is convenient to divide the causes of portal hypertension into those produced within and without the liver (Table 1).

In general, the extrahepatic causes are clearly understood, at least in terms of mechanics, and relatively infrequent in occurrence. The intrahepatic causes produce more than 90 percent of all portal hypertension, and in the United States cirrhosis of the liver associated with excessive alcohol intake is the most commonly seen. Our understanding of the pathophysiology of portal hypertension which originates from disease within the liver is still largely theoretical and is being modified almost constantly.

It is ordinarily possible on clinical grounds alone to distinguish between extrahepatic obstruction to blood flow that occurs before the entry of the portal circulation into the liver, and the obstruction that impedes egress of flow from the liver. When portal vein obstruction exists as an

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TABLE 1.—*Classification of Portal Hypertension*

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- I. Extra Hepatic
- A. Obstruction to venous outflow above the liver
 1. Budd-Chiari Syndrome (hepatic vein thrombosis, e.g., primary hepatic or metastatic tumors; polycythemia; thrombophlebitis migrans)
 2. Obstruction of venous outflow through the suprahepatic vena cava (e.g., constrictive pericarditis; tricuspid insufficiency; chronic congestive heart failure; tumors; congenital abnormality of the vena cava)
 - B. Obstruction to portal venous inflow below the liver
 1. Congenital (cavernomatous transformation, atresia, stenosis)
 2. Thrombosis (e.g., pylephlebitis due to neonatal omphalitis or intra-abdominal infection; trauma; polycythemia)
 3. Compression (e.g., tumors, pancreatitis)
 - C. Arterio-portal fistula (e.g., hepatic artery-portal vein or splenic artery-splenic vein fistula following trauma or ruptured aneurysm)
- II. Intrahepatic
- A. Cirrhosis
 1. Laennec's (alcoholic, nutritional)
 2. Post-necrotic (posthepatic)
 3. Biliary (following chronic bile duct obstruction)
 - B. Other forms of fibrosis (congenital cystic liver, sarcoidosis, polycystic disease, syphilis, schistosomiasis, hemachromatosis)
 - C. Tumors (neoplasm or granuloma)
-

isolated phenomenon, hepatocellular function is usually preserved and ascites is rare. However, when obstruction occurs at the level of the hepatic veins or above, the resulting elevation in pressure is transmitted back to the sinusoids of the liver, resulting in a decided increase in lymph formation and the development of ascites (hepatocellular function in these circumstances is quite likely to show impairment). Disturbances of circulation within the liver produce clinical symptoms which may mimic those associated with either form of extrahepatic obstruction and may often represent hemodynamic elements of both.

In order to appreciate the multiple factors at play in the development of portal hypertension from intrahepatic causes, an understanding of the structure of the hepatic parenchyma is essential. The portal venous tree branches to an extraordinarily high degree¹ to empty blood directly into the hepatic sinusoids. In addition, tiny branches of the hepatic artery enter either portal venules or connect directly with the sinusoids. The sinusoidal bed is a continuous meshwork of interconnected blood spaces into which is interposed an equally continuous system of sheets and beams of liver cells lined by a delicate endothelial cell sheet.²

Thus, it is theoretically possible for blood cells to travel about in the sinusoidal system in response to prevailing pressure gradients. In addition, blood flow is not constant in all sinusoids at a given moment. It is believed, for example, that in the fasting state less than two-fifths of the sinusoids convey blood and, in response to increased hepatic blood flow, additional sinusoids open.³ Hence the resistance to flow through the sinusoidal bed is not constant and a two-fold increase in liver blood flow increases portal pressure by much less than a factor of two.⁴ It seems clear that distortion of normal hepatic architecture by the cirrhotic process tends to impair the ability of the sinusoidal bed to accommodate increases in blood flow with only mild elevation of perfusion (portal) pressure, but the total contribution of this mechanism to the magnitude of portal hypertension is unknown.

The connective tissue of the liver forms the scaffolding upon which parenchymal cells and vascular elements are suspended. This may be roughly divided into the lobular, vascular and capsular portions. The major amount of this collagen and reticulin framework, apart from that comprising Glisson's capsule, invests blood vessels larger than the sinusoids.⁵ In addition, microscopic studies suggest that the central vein of the liver lobule is poorly supported by connective tissue, which only appears in significant amounts in the hepatic vein system several orders of branching beyond the central vein.⁴ Thus, the proximal efferent hepatic vascular tree would seem to be especially susceptible to compression or collapse resulting from lateral pressure applied to its walls.

One of the most constant hemodynamic observations in patients with cirrhosis, whether of alcoholic, nutritional or postnecrotic type, has been elevation of the wedged hepatic vein pressure. The pressure within the large hepatic veins is only somewhat higher than the pressure within the inferior vena cava. However, a small intravascular catheter, introduced through an hepatic vein and advanced to the point at which it totally occludes a smaller hepatic vein, transmits pressure through an open tip which is believed to reflect pressure distal to the end of the catheter. Pressure measured in this fashion is believed to rise until blood can flow or "run off" through the anastomotic channels at the level of the sinusoids. Since, in a given patient with cirrhosis, the wedged hepatic vein pres-

sure differs only slightly from pressure measured within the portal vein, the obstruction to hepatic blood flow is said to be "postsinusoidal." In fact, however, it has not been possible to measure differentially the amount of obstruction to flow contributed by the small portal venules, the sinusoids, and the smallest hepatic venules.

Although the anatomic basis of postsinusoidal block is unclear, much has been inferred from the microscopic appearance of hepatic cirrhosis. Characteristically, what may be seen is fibrosis of the periportal region, lesser degrees of fibrosis of the hepatic venous region, reduction in number of both portal and hepatic venules, and distortion of the hepatic architecture with scarring and formation of regenerative nodules. Electron micrographs demonstrate deposition of collagen in the space of Disse, the area between the endothelial lining of the sinusoids and the liver cells, through which the transport of metabolites is believed to occur.

Based on microscopic observations such as these, Popper and Schaffner⁶ have set forth an hypothesis to explain the postsinusoidal elevation of portal pressure in cirrhosis. The regenerative nodule forms in the cirrhotic liver, and develops by pushing back the surrounding thickened, fibrous tissue of the portal tracts and the adjacent scar tissue. New hepatic veins and portal veins do not grow within this nodule, but are splayed out over the surface of the nodule, where they connect with its sinusoids. Compression of these vessels by continued growth of the regenerative nodule against the rigid scar results in postsinusoidal portal hypertension.

Although the foregoing explanation would seem to suffice for most cases of cirrhosis with portal hypertension, there are a few cases in which very mild degrees of hepatic damage contrast with striking elevations of portal venous pressure.^{7,8} To account for these variant cases and also provide an alternative to the accepted causative factors in portal hypertension, Shaldon⁹ suggested that humoral factors may be of considerable importance, and pointed out that both epinephrine and norepinephrine may cause obstruction to hepatic venous flow within the liver. Other investigators, however, have been unable to confirm his observation of elevated catecholamine levels in the portal venous blood of patients with portal hypertension.¹⁰ Thus, the influence of these agents in the development of portal hypertension remains obscure.

Other observers have called attention to patients with unexplained portal hypertension coexisting with near-normal hepatic architecture and function in whom the portal vein was patent.^{11,12,13} Mikkelsen and colleagues¹⁴ reported 17 such patients in whom they found subtle sclerotic changes in the tiny portal veins. They contrasted this microscopic pattern with that noted in other groups of their patients who had either partial or total occlusion of the extrahepatic portal vein, and concluded that all seemed to have the same underlying etiologic mechanism, namely phlebosclerosis of the portal venous system. Wedged hepatic vein pressure was measured in only three of the 17 patients with patent portal veins, but it was found to be normal in each instance, supporting the microscopic observation of a presinusoidal block.

In addition to an increased hepatic resistance to blood flow, changes in the arterial supply to the liver in cirrhosis have been thought to contribute to the development of portal hypertension. In 1952 Popper, Elias and Petty¹⁵ showed that as cirrhosis advances, the number of connections between the hepatic arterioles and the portal venules increases. The idea that a portion of hepatic arterial pressure might thus be transferred directly to the portal vein was further supported by subsequent reports of the development, in man, of portal hypertension and esophageal varices resulting from a fistula connecting the hepatic artery with the portal vein.^{16,17} Considerable evidence casts doubt on the direct contribution of hepatic arterial pressure to portal hypertension in the cirrhotic patient. The possibility of an increase in portal pressure, as the result of increased blood flow through the liver, is unlikely in view of the general observation of investigators of a diminution in total hepatic blood flow in cirrhosis.^{18,19} Warren and Muller,²⁰ in a study of the hemodynamic responses to side-to-side portacaval shunting in portal hypertensive patients, found no loss of significant amounts of saturated blood into the portal vein after the shunting, and no decrease in the oxygen saturation of hepatic vein blood. These data, of course, are not consistent with the concept that small hepatic arteriovenous fistulae pour large amounts of blood into the portal venous system.

The development of intrahepatic portal hypertension may currently be viewed as a complex process in which structural alteration of portal venules, sinusoids, and hepatic venules causes pro-

nounced changes in liver hemodynamics. Whether these structural changes precede, accompany or result from metabolic alterations in the liver cells is unknown. However, it seems reasonable to speculate that the abnormalities in liver circulation are not entirely the result of pathologic processes but may be due, in part, to compensatory mechanisms, the purpose of which is to ensure continuing transfer of metabolites between the circulation and the hepatocytes. The rapid deterioration of liver function occasionally seen following sudden portal decompression tends to support this conjecture.

Complications of Portal Hypertension

The Natural History of Variceal Hemorrhage

The prevalence of esophageal varices within the general population is unknown, since cirrhosis or portal hypertension, of themselves, may produce no symptoms sufficiently disturbing to cause the affected person to seek medical care. Thus, a true picture of the natural history of esophageal varices is difficult to perceive, since most patients in whom the diagnosis can be made will be drawn from the group having some additional complication such as ascites or variceal hemorrhage, or some manifestation of liver decompression, such as jaundice or encephalopathy.

Most of the reported series deal largely with patients who have one or more of these complications and there is no doubt that the outlook for these persons is bleak. Mortality rates for variceal hemorrhage range from 40 percent to 80 percent on the average, depending upon the clinical condition of the patients and the type of therapy provided.¹⁰ This is not to say, however, that all patients with varices face an imminent threat of hemorrhage and this very poor prognosis. Baker and colleagues²¹ observed 115 cirrhotic patients in whom varices were diagnosed before bleeding occurred. The follow-up period for this group was from two to ten years (mean 3.3 years), and it was noted that only 33 (28.5 percent) had hemorrhage during that time.

The precipitating causes of esophageal varix rupture remain obscure. Any theory of pathogenesis must, of course, account for the fact that rarely, except from direct trauma, do portosystemic varicosities in other locations, such as the retroperitoneal area and the hemorrhoidal or umbilical plexus of veins, rupture to bring about significant hemorrhage. Trauma to esophageal varices might be produced more subtly, however,

and for a long time it was thought that coarse food might abrade or weaken the walls of these friable vessels, provoking hemorrhage. This is no longer considered a primary cause in most instances of varix rupture. Certainly, it is much more common to obtain a history of ingestion of liquids (mostly alcoholic) than of rough solids as a precursor to hematemesis, and also it is observed that many persons with varices take their usual diet for long periods without the occurrence of hemorrhage.

With respect to trauma, peptic esophagitis was also formerly thought to play a significant role in the precipitation of hemorrhage. The evidence favoring this theory is mainly based upon autopsy findings, of lower esophageal erosions in patients who died of variceal hemorrhage. A pertinent study was conducted by Orloff and Thomas,²² who examined the lower esophagus of 18 patients at the time of emergency operation for ligation of varices to stop hemorrhage. In only one patient was there evidence of peptic esophagitis. These investigators also cited additional strong evidence against the regular participation of esophagitis in variceal rupture.

Perhaps the most widely held notions about variceal rupture are embodied in the hydrostatic pressure hypothesis. Liebowitz lucidly set forth the evidence favoring this theory in his 1961 review of the topic²³ and emphasized the following features as provocative of variceal hemorrhage: the structure of esophageal varices, their location within the thorax, and the influence of forces acting on their walls as described by the physical laws governing the flow of fluid in tubes.

Varices develop in response to increased intraluminal pressure transmitted through collateral channels by the hypertensive portal bed. According to the Laplace relationship, the tension on the wall of a distensible tube equals the product of the radius of the tube and the pressure on its wall. Thus, as the veins in the submucosa of the lower esophagus dilate in response to the increased tension on their walls, progressively less pressure development is required to further increase wall tension and hence dilatation. Blackburn²⁴ used the analogy of the balloon—the bigger it gets, the easier it is to blow up.

The early and extensive development of varices in the cardio-esophageal area may be accounted for by the direct route of drainage from the major portal vessels through the coronary vein and vasa

brevia, as opposed to the longer and less direct routes to the more remote portal-systemic junctions. In addition, the loose areolar tissue in which the esophageal veins are suspended, and the generally elastic surrounding tissues of the esophagus, do not provide a very effective barrier against dilatation. Finally, the consequences of exposure to negative intrathoracic pressure bring about a pronounced increase in the pressure gradient across the walls of an esophageal varix and hence produce greater wall tension than that ordinarily existing in any extrathoracic portal collateral varix.

Increasing tension on the wall of a varix is associated with striking structural changes. The wall becomes thinned out, smooth muscle and elastic tissue are replaced by scar, and the "elastic limit" is reached. The esophageal mucosa may disappear over the varix whose walls become the lining of the esophagus. Liebowitz²³ aptly termed this state "but one step removed from actual bursting of the vein wall."

Physiologic acts, such as coughing, vomiting, and straining have been often noted clinically to precede variceal hemorrhage.²³ Sudden elevations of intraabdominal pressure are, of course, transferred directly to the portal circulation and, thus, through the collateral channels to the varices. If, at such a moment, intrathoracic pressure is less than intraabdominal pressure, the gradient across the varix wall will be enhanced by the amount of the difference, and forces of considerable magnitude will be acting to promote rupture.

Finally, it is our impression, shared by other observers,^{21,26} that variceal hemorrhage is more likely to occur during periods of acute liver decompensation. This is manifested in the alcoholic group by the patient who has hemorrhage during an intercurrent spree or binge, perhaps in response to a sudden increase in portal pressure. Objective evidence to support this must await the development of a technique to monitor portal pressure of the patient in his usual environment.

Variceal Hemorrhage— Nonoperative Management

Two approaches have been utilized for the nonoperative control of variceal hemorrhage: compression of varices by means of balloon tamponade and reduction of splanchnic (and hence portal) collateral blood flow by administration of vasoactive drugs or by gastric hypothermia. It is now

generally recognized that all nonoperative measures are only temporarily effective and that prevention of recurrent bleeding can only be regularly achieved by performance of an operation which will decompress the portal bed into the systemic circulation. The proper function of temporary measures is to obtain time for the planning and execution of definitive treatment under the most favorable circumstances possible. Each of these measures carries its own unique set of benefits and hazards, and selection of one method or another depends upon the amount of time required to achieve an optimal state in a given patient and the "risk" incurred in gaining this time as weighed against the effectiveness and complications of the technique.

Since the publication of the report of Sengstaken and Blakemore²⁷ in 1950 the triple lumen, double balloon tube has been used extensively throughout this country for the initial control of variceal hemorrhage. Other balloon tubes of modified design^{28,29} have been described, but their advantages in general use have never been great enough to permit them to supplant the Sengstaken-Blakemore tube. Although the principles underlying the use of this tube are readily understood, skill in its management is not spontaneously acquired. In addition to failure to control hemorrhage, the tube may itself pose direct hazards to the patient. Conn³⁰ wrote of nine deaths in a group of 50 patients undergoing esophageal tamponade that were attributed directly to use of the technique and emphasized the following complications: Airway obstruction due to displaced balloons; aspiration of secretions with pneumonitis; and problems from overinflation of the balloons. We have found that emphasis of the following points has aided our house officers in avoiding these difficulties: the Sengstaken-Blakemore tube is never inserted until its balloons have been tested under water for leaks. Concurrently the gastric and esophageal balloons are inflated to their desired diameters and the reading of the aneroid manometers noted. Inflation under pressure is maintained for a few minutes. Loss of pressure in the system indicates a leak and all joints and valves are then checked and tightened or replaced as necessary. With the system competent, inflation to the predetermined levels of pressure will ensure the desired balloon expansion, and the manometer readings are monitored by the attending nurses to ensure maintenance of balloon tension.

Since the esophageal balloon makes the swallowing of secretions impossible, they must be continuously removed lest they be aspirated into the lungs. A sump tube inserted into the upper esophagus and attached to continuous suction is effective for this purpose. Oropharyngeal and orotracheal suctioning are also employed frequently following insertion of the tube, and if much material is recovered, especially in the comatose or uncooperative patient, tracheostomy is performed to facilitate removal of tracheopulmonary secretions.

After insertion of the tube and inflation of the balloons an x-ray film showing the lower chest and upper abdomen is obtained and the lucencies of the balloons checked for proper position. It is usually possible to allow the tube to remain in place and undisturbed for two or three days but if longer intubation is required the balloons should be deflated periodically to avoid ischemic necrosis of the adjacent mucosa.

The tube is fixed to a cord passed over a single pulley attached to the end of the bed. From the cord is suspended a weight of a half pound to a pound. This suffices to maintain the position of the balloon, collapse varices on the gastric side of the gastroesophageal junction, and prevent the tube from becoming entangled with the patient or his surroundings. The role of traction in the arrest of hemorrhage is controversial but we have not seen continuing hemorrhage controlled by the addition of more weight to a properly positioned and properly inflated tube. The tube must, of course, be led from the nose in a direct line to the pulley so as to avoid pressure on the nasal cartilages and subsequent necrosis.

Numerous devices have been introduced for replacement of the single cord and pulley system.^{31,32} In general these consist of a helmet or face mask with an attached spring or motor to which the tube is fixed. The advantages from use of these devices include ease in positioning the tube to avoid nasal cartilage injury, freedom of patient movement, and prevention of tube dislodgment in the agitated patient.

Patients undergoing balloon tamponade must receive constant skilled nursing care, preferably in an intensive care unit. We generally deflate both balloons after 48 hours and if no further bleeding occurs we remove the tube after another 24 hours. If bleeding recurs, balloon tamponade is immedi-

ately resumed. To prevent re-use, balloons are cut in two upon removal.

Vasopressin (Pituitrin,[®] Pitressin[®]) has long been recognized as possessing a potent vasoconstrictive effect in the splanchnic arterial circulation and has been shown capable of lowering both portal pressure and blood flow. A number of reports have described the use of this agent in the control of variceal hemorrhage.^{33,34} Although initial control of hemorrhage is frequently achieved, the effects are transitory, lasting from a few minutes to a few hours after administration, and the incidence of rebleeding is high, 63 percent in the series of Shaldon and Sherlock³⁵ and 83 percent in the larger group of patients reported by Orloff.³⁶

Prolonged control of variceal hemorrhage by continuous infusion of vasopressin into the superior mesentery artery was described by Nussbaum and coworkers³⁷ in two patients. The electrocardiogram and urinary output were carefully monitored and no untoward effects were noted. Infusion of other vasoactive agents has also been employed in attempts at pharmacologic control of variceal hemorrhage. Kuhn and coworkers³⁸ reported cessation of hemorrhage in six patients treated by controlled systemic hypotension brought about by infusion of a ganglionic blocking drug, Arfonad.^{®*} Although intravenous vasopressin administration seems to offer effective short-term control or diminution of variceal hemorrhage, we have been reluctant to employ it regularly because of its known coronary vasoconstrictive properties and because we have come to rely upon the Sengstaken-Blakemore tube for initial control of bleeding. Further experience with continuous splanchnic arterial infusions of this drug and with other drugs is required before a valid comparison can be made with the other nonsurgical techniques.

Esophagogastric cooling has been introduced as a new method for control of variceal hemorrhage. Wangenstein and associates³⁹ reported upon 22 patients with esophageal varices who were bleeding treated by means of circulating liquid at near-freezing temperatures through a large gastric balloon. Hemorrhage was arrested in all patients, seven of whom had had an unsuccessful trial of balloon tamponade. Fifteen of the 22 patients subsequently died, nine from liver failure preoperatively and six following operation. Gastric hypothermia is known to reduce acid-peptic activity and

*Trimethaphan.

TABLE 2.—Clinical State of Cirrhotic Patients as Related to Hepatic Reserve

<i>Clinical Observation</i>	<i>Hepatic Reserve</i>		
	<i>Good</i>	<i>Fair</i>	<i>Poor</i>
Serum Bilirubin (mg per 100 ml)	<2.0	2.0 - 3.0	Over 3.0
Serum Albumin (gm per 100 ml)	>3.5	3.0 - 3.5	<3.0
Ascites	None	Minimal; easily controlled	Poorly controlled
Neurological Signs	None	Minimal	"Coma"
Nutrition	Good	Good	Wasting

decrease gastric blood flow. Beyond these effects little is known of the changes that may occur in the hypertensive portal circulation. More experience is required before the proper place of this technique in the control of variceal hemorrhage can be determined. Ritchie and coworkers⁴⁰ reported the use of gastric freezing in ten patients with bleeding esophageal varices, apparently with benefit, but they gave no details in their paper.

Operative Management of Variceal Hemorrhage

That construction of a large functioning shunt between the portal and systemic venous circulations is the most effective means by which recurrent variceal hemorrhage may be prevented has been repeatedly documented in the literature of this subject over the last 20 years. Although most patients survive such operations to enjoy the benefits of protection from bleeding, others are unable to withstand the rigors of operation and die in the postoperative period, usually with liver dysfunction dominating the situation. To determine with some degree of reliability both benefit and risk of operation in the individual patient, much attention has been focused on three areas: the clinical state of the patient, the timing of intervention, and the type of portal decompression to be effected.

Clinical Classification Of Cirrhotic Patients

It has become abundantly clear as operative experience with portal hypertensive patients has accumulated that the risk of any procedure to effect portal decompression is directly related to hepatic functional reserve. Thus, in order to make valid comparisons between various operations in various series of patients, knowledge of the clinical state and an estimate of hepatic reserve are required. Information of this type was frequently lacking from the early reported experience, making comparisons difficult and tending to make portal decompression seem more dangerous than it is. Of late, authors have included clinical and laboratory descriptions

of their patients and consequently a clearer picture of the risks of portal decompression has emerged. Employment of a clinical classification has been found to be of considerable benefit in treating the cirrhotic patient because it facilitates both the planning of therapy and the making of clinical decisions.

Several such systems have been advocated, but because of its simplicity and because more complicated evaluations have not provided additional insight we employ a classification similar to that described by Wantz and Payne⁴¹ and Child and Turcotte¹⁰ (Table 2). Subsequent discussion of mortality following operation will be set forth in the light of our interpretation of how patients in the various reported series might fit into such a classification. A scheme of this type is useful in assessing operative risks at a given time in the clinical course of the patient's disease, but is less helpful in establishing an ultimate prognosis. Here many other factors come into play—for example, the pattern of alcoholic intake, nutritional habits and work history, to mention but a few. As a general rule patients with "good" to "fair" liver reserve tolerate portal decompression well with small risk, while postoperative mortality rates among those with "poor" reserve are very high. A point of some importance, however, is that these clinical states are seldom static and that it is often possible through intensive medical treatment in the hospital, for a period of weeks or months, to convert a patient from the "poor" to the "fair" or from the "fair" to the "good" category. This observation bears relevantly on the timing of operation.

The Timing of Portal Decompression

Three broad groups of patients are generally considered for shunt operations, and these are, in order of frequency: (1) Patients who have survived one or more hemorrhages but are not actively bleeding; (2) patients who are actively bleeding or in whom bleeding is controlled by nonoperative means; (3) those with varices which have never bled. Thus if a shunt were to be performed in each

TABLE 3.—*Postoperative Mortality in Patients Undergoing Elective Portal-Systemic Shunt in Selected Series*

No. Patients	Clinical Classification						Total Mortality (%)	Year	Authors (Ref.)
	Good		Fair		Poor				
	# Pts.	% Mortality	# Pts.	% Mortality	# Pts.	% Mortality			
97	41	2.4	39	12.8	17	29.4	11.3	1961	Wantz and Payne ⁴¹
104	60	..	34	...	10	...	14	1963	Rousselot et al ⁴²
92	..		Unclassified			...	5.4	1964	Brick and Palmer ⁴³
128	48	0	46	9	34	53	17	1964	Child and Turcotte ¹⁰
87	..		Unclassified			...	26.4	1965	Satterfield et al ⁴⁴

TABLE 4.—*Postoperative Mortality in Patients Undergoing Emergency Portal-Systemic Shunt in Selected Series*

No. Patients	Clinical Classification (# Pts.-% Mortality)			Total Mortality (%)	Type Hospital	Year	Authors (Ref.)
	Good	Fair	Poor				
37		18.0%	19-68%	35%	Private and University	1962	Mikkelsen ⁴⁶
18		Unclassified		38.8%	Military and University	1964	Brick and Palmer ⁴³
17		Unclassified		23.5%	University	1964	Ekman and Sandblom ⁴⁷
13	11		2	23%	University	1964	Peskin et al ⁴⁸
30	All good to fair			26.7%	Private Clinic	1967	Adson ⁴⁹
40		Majority fair to poor		47%	City	1967	Orloff ⁴⁵

group it would be termed respectively, elective, emergency, or prophylactic.

Table 3 is a compilation of several large series of electively performed shunt operations, and the postoperative mortality rates are noted to range from 5 to 26 percent, seemingly a considerable spread. However, when one considers the clinical classification of patients making up several of these series and notes the generally low mortality rates for patients with good or fair liver function (0 to 13 percent) as opposed to those with poor liver function (29 to 53 percent), an accounting of the number of patients in each group seems to resolve the discrepancy. We therefore recommend portosystemic decompression for patients with "good" hepatic reserve and for those with "fair" reserve after a period of intensive medical treatment aimed at improving liver function. In addition, operation may be offered to selected patients in the "poor" reserve group if intensive medical management brings about some improvement in liver function—for example, clearing of neurological signs, pronounced diminution or disappearance of ascites, fall in the serum bilirubin, and gain in serum albumin concentration. We try to avoid operation in the "dead end" cirrhotic patient whose liver function either does not improve or declines further with medical treatment.

When a shunt operation is done to arrest acute

variceal hemorrhage it is termed an "emergency" shunt. Preliminary treatment varies widely, however, among surgeons. Child and coworkers¹⁰ employ balloon tamponade and supportive treatment for a period of 12 to 48 hours before operation whereas Orloff⁴⁵ uses vasopressin infusion with volume restoration and other supportive measures while the diagnostic workup is conducted and then performs operation within eight hours. Table 4 is a compilation of results in the treatment of variceal hemorrhage by emergency portal decompression. It may be seen once again that patients with good or fair liver function tolerate operation relatively well while patients with pronounced liver impairment do poorly. Total mortality rates seem to be a function of the clinical status of the group of cirrhotic patients under treatment and thus it is not surprising to find considerable differences in mortality between the mainly good and fair reserve private clinic patients in Adson's series⁴⁹ and the mainly poor reserve city indigent patients reported by Orloff.⁴⁵ It should be added in this connection that Orloff's report contains a comparative analysis of the results of emergency shunt, varix ligation, and nonoperative treatment of variceal hemorrhage in comparable groups of patients from a single institution and reveals a similar mortality for varix ligation (46 percent) and emergency portacaval shunt (47 percent) compared with an 83 percent mortality with nonoperative treatment.

The term "emergency shunt" is a misleading one because from it is sometimes inferred a situation in which the patient is rushed to the operating room with active and uncontrolled hemorrhage and little preoperative preparation. The "emergency shunt" has seldom been employed in this fashion. The term "urgent shunt" seems to us more appropriate because it implies control of hemorrhage by balloon tamponade or other nonoperative techniques, restoration of blood volume deficits, and reversal or improvement of acid-base abnormalities preoperatively. Moreover, an "urgent shunt" is not a precipitous act but one that is taken deliberately, sometimes in a few hours and at others in a period of days.

We consider good and fair risk patients for urgent portal decompression, believing the risk of operation to be little greater than in the same patients operated upon electively. Poor risk patients are treated nonoperatively if control of hemorrhage can be achieved, and intensive medical therapy aimed at improving liver function is instituted. If bleeding remains uncontrolled in this group, a transthoracic ligation of varices is performed.

Should cirrhotic patients with esophageal varices that have never bled be offered prophylactic shunt to prevent variceal hemorrhage? Formerly it was not known which was the greater, the risk of operation or the risk of hemorrhage. Several controlled investigations^{50,51,52} have illuminated this subject. These studies confirm the observation that variceal hemorrhage is rare in the presence of a functioning portacaval shunt. Mortality rates following prophylactic shunt are comparable to those after elective shunt and depend upon patient selection. Demonstrable varices disappear in a high proportion of patients following prophylactic shunt. Sequelae of portal decompression, such as encephalopathy, seem to occur with about equal frequency in shunted patients and nonshunted controls. However, the severity of these disorders appears to be greater in the shunted group. Finally, allowing for differences in experimental design and patient populations, it is becoming increasingly apparent that long-term survival is not increased by shunt operation in unselected cirrhotic patients with esophageal varices, despite the fact that the incidence of hemorrhage is decidedly reduced. There is need for the development of criteria which will permit the identification of patients who have not bled but who are likely to do so. Cur-

rently we accept for prophylactic portal decompression all patients with good hepatic reserve and some with fair reserve. In the remainder, the risk of operation seems to outweigh the risk of hemorrhage and thus operation is not offered.

The Selection of Operation

The operative procedure which has probably been performed most frequently to effect portal decompression is anastomosis of the caudal end of the portal vein, which has been divided at the hilum of the liver, to the antero-medial side of the adjacent inferior vena cava. Such an end-to-side shunt completely abolishes hypertension in the splanchnic venous system, while sinusoidal pressure within the liver (as reflected by wedged hepatic vein pressure) usually remains about the same. Equally effective decompression of the splanchnic bed is achieved by anastomosis of the portal vein to the inferior vena cava in a side-to-side fashion without proximal ligation of the former, and this results regularly in a decrease in wedged hepatic vein pressure, although not usually to normal levels. It is generally agreed that these two types of shunt are about equally effective in controlling acute, or preventing recurrent, variceal bleeding. Occasionally the presence of an enlarged caudate lobe of the liver, scarring in the porta hepatis, or an aberrant course of the hepatic artery may render side-to-side anastomosis technically difficult. Some surgeons prefer to perform a side-to-side anastomosis if significant ascites is present, believing that decompression of the sinusoids is beneficial in reducing the contribution of liver lymph to abdominal fluid accumulation, notwithstanding the observation that ascites is often noted to disappear following the performance of an end-to-side shunt. Wolfman and associates⁵³ presented evidence from a controlled study of both types of shunt that greater improvement in urinary sodium excretion follows side-to-side anastomosis, and on this basis and other clinical observations⁵⁴ we favor its application in the ascitic patient. A possible disadvantage of the lateral shunt has been raised by the study of Zuidema and Kirsh⁵⁵ which suggests that the incidence of hepatic encephalopathy is greater than it is after other varieties of portosystemic shunts.

Finally, Turcotte and coworkers⁵⁶ reported a series of 102 patients with comparable numbers receiving shunt of one or the other type and noted a significantly lower operative mortality in the poor

risk patients undergoing lateral anastomosis (7 of 19 patients or 39 percent) than in those in whom end-to-side shunts (14 of 20 patients or 70 percent) were constructed. No important differences were noted between good risk and fair risk patients in this series. Since randomization was not carried out before operation, and recognizing that there is often considerable difference in the ease with which each type of shunt may be constructed, bias may have weighted the results; and thus the observation as to the safety of one shunt or another in poor risk patients, although provocative, is not conclusive.

The splenorenal shunt, constructed by means of anastomosis of the divided distal end of the splenic vein to the superior side of the left renal vein, has been particularly useful in the treatment of portal hypertensive patients whose portal vein is occluded by thrombus. Linton⁵² reported extensive experience with this operation for portal decompression and expressed belief that it is associated with a lower incidence of encephalopathy than is portacaval shunt. Technically this procedure is more difficult to perform than either variety of portacaval shunt, and the size of the anastomotic junction is limited by the diameter of the splenic vein. McDermott and coworkers⁵⁴ showed that portal pressure falls significantly less after splenorenal than after portacaval shunt, and this, coupled with a greater tendency for thrombosis at the anastomosis, is believed to account for an increased incidence of recurrent hemorrhage following splenorenal shunt.

Anastomosis of the distal end of the divided inferior vena cava to the side of the superior mesenteric vein was described independently by Clatworthy and Boles⁵⁸ in this country and Marion and coworkers⁵⁹ in France. It is especially useful in patients with extrahepatic portal block, and often it is the only alternative when both portal and splenic veins are not patent.

Although many persons lead apparently normal lives following portal decompression, there is little evidence that longevity is increased in cirrhotic patients undergoing this procedure, and furthermore there exists the impression that a decline in liver function is accentuated in some patients after portacaval shunt. Warren in a recent report⁶⁰ emphasized the limitations of current techniques in identification of such persons but suggested that the portal hypertensive with high residual blood

flow through the portal vein into the liver is particularly susceptible to encephalopathy and liver dysfunction following portacaval shunt. In an attempt to preserve portal blood flow and protect liver function while bringing about selective decompression of gastroesophageal varices, he introduced a type of spleno-renal shunt which is intended to effect transsplenic decompression of gastroesophageal varices. In addition, ligation of the coronary vein and partial devascularization of the stomach by ligation of the left gastric artery are performed. Other forms of a "lesser shunt" combined with devascularization techniques have been described^{61,62} and although the therapeutic aims of all these procedures are commendable further clinical experience is required to demonstrate that the risk of recurrent hemorrhage following their employment is truly less than that of shunt-associated hepatic dysfunction.

Devascularization procedures without concomitant portal decompression in the treatment of portal hypertension have been advocated for many years, mainly by Womack and Peters whose most recent results are contained in the report of Johnson and coworkers.⁶³ Although operative mortality was high (24 of 51 poor risk patients and 27 of 51 operated upon in emergency) and continued bleeding or rebleeding fairly frequent, overall five-year survival was comparable to that following portal decompression reported in other series and death due to liver failure was rarely seen. We have no personal experience with intra-abdominal devascularization procedures and, while acknowledging that some patients might benefit, we are unable to predict which ones.

Intolerance of the patient with poor hepatic reserve to any major operative procedure continues to stimulate investigation of new surgical techniques for control of variceal hemorrhage that do not require prolonged and extensive operations. The demonstration by Gonzalez-Carbaheas⁶⁴ that the umbilical vein of the adult human may be reopened into the portal vein for the performance of portography suggested to several investigators that the portal bed might be successfully decompressed via this route. Subsequently Piccone and LeVeen,⁶⁵ Christopherson and coworkers,⁶⁶ and White and associates⁶⁷ each described systems for transumbilical portal decompression through an external shunt into the systemic venous circulation via a superficial vein. External pumps have been

utilized in these systems; and adequate flow rates have also been achieved by utilizing only the portal to systemic pressure gradient. Thrombosis of the shunts has reportedly not been a major problem, although in all instances they have been used only temporarily; none has remained in place longer than five days. Reduction in portal pressures and cessation of variceal hemorrhage have been reported. Potential hazards include infection and thrombosis of the portal vein. This technique would appear to merit further investigation in patients not suitable for emergency portacaval shunting.

Another approach has incorporated thoracic duct lymph drainage, which has been reported to reduce portal pressure and control hemorrhage from varices.⁶⁸ A recent report,⁶⁹ however, provides evidence that this pressure reduction may be merely a reflection of hypovolemia and cautions that serious hemodynamic and metabolic problems may be precipitated by thoracic duct drainage without circulatory replacement of fluid and protein in cirrhotic patients.

Cirrhotic Ascites

Pathophysiology

A survey of the literature in this complex and incompletely understood topic is far beyond the scope of this report. Acknowledging that generalizations in this area tend toward oversimplification and that paradoxes outnumber consistencies, the following description is offered.

It is generally believed that in the majority of cirrhotic patients the development of ascites is primarily evoked by mechanical obstruction to the outflow of blood from the liver through the hepatic veins. With reference to the hepatic parenchyma the block is said to be "postsinusoidal." Two readily observable clinical situations in noncirrhotic persons are in accordance with this view: supra-diaphragmatic constriction of the inferior vena cava, which is often associated with ascites, and extra-hepatic portal vein thrombosis which is rarely so.

The hepatic generation of ascitic fluid is thought to occur when pressure in the sinusoids reaches a critical level as to both hydrostatic and colloid osmotic components. At this point the amount of fluid transudate entering the perisinusoidal space of Disse exceeds the capacity of the efferent lymphatics of the liver and extravasates through the liver capsule into the abdominal cavity as ascites.

Much attention has been focused on the importance of the hydrostatic pressure within the sinusoids to the production of ascites. However, of perhaps equal importance is the level of plasma colloid osmotic pressure. The Starling relationship⁷⁰ governing the transfer of fluids across capillary walls states that net transfer of fluids is determined by two opposing forces, the hydrostatic pressure of the blood promoting outward movement of fluid and the osmotic pressure of blood promoting inward movement of fluid. Atkinson and Losowsky^{71,72} expressed this relationship with respect to the formation of ascites in the following formula:

$$\frac{10 \times \text{serum albumin (gm per 100 ml)} + 4}{\text{Intrasplenic pressure (cm H}_2\text{O)}} = \begin{matrix} \text{about 5 (normal)} \\ \text{less than 1 (ascites)} \end{matrix}$$

Thus ascites production in a given cirrhotic patient depends upon both the degree of portal hypertension (insofar as it truly reflects sinusoidal hydrostatic pressure) and the serum concentration of albumin (plasma colloid osmotic pressure).

Several factors act to reduce albumin concentration in cirrhotic patients. The damaged liver synthesizes less albumin than normal and the rate of breakdown of albumin may be accelerated. In addition the increase in total body water accompanying ascites tends to produce dilutional hypoalbuminemia.

During the last decade much new information has been gained concerning the relationships of liver disease to abnormalities of salt, water and adrenal steroid metabolism.⁷³ Among the pertinent observations has been the demonstration by Schedl and Bartter⁷⁴ that impaired water diuresis, following water-loading in certain cirrhotic patients, is not due primarily to retention of water caused by increased sensitivity or production of antidiuretic hormone but rather to excessive reabsorption of sodium in the proximal renal tubule where reabsorption occurs isotonically with the glomerular filtrate. Consequently only small volumes of free water can be generated in the distal renal tubule. The pronounced tendency for resorption of sodium ions in the proximal renal tubule is presumed to be due in part to increased production or diminished degradation of aldosterone.

Hyponatremia frequently accompanies ascites and thus it seems that water retention on occasion may exceed sodium retention, although the mechanisms by which this is accomplished are not well defined.⁷⁵

Medical management of ascites has gained in effectiveness in recent years mainly as a result of the introduction of diuretic agents such as chlorothiazide and drugs which antagonize the sodium-retaining properties of aldosterone, particularly spironolactone. These agents are especially useful when older and safer methods, such as bed rest, nutritious diet and restriction of sodium and water fail to bring about resolution of ascites. The former practice of frequent paracentesis is now recognized not only as useless but actually detrimental, because of the resultant decrease in circulating blood volume and serum proteins. Other medical measures occasionally employed include urine acidification, adrenal steroids, infusions of human serum albumin, and limited paracentesis.⁷⁶

With the introduction of ever more potent diuretic agents some physicians have come to express skepticism that truly medically refractory ascites exists as a clinical entity. Proving this point in some cirrhotic patients with ascites can tax renal reserves to the point of no return. Moreover, the maintenance of acid base balance and plasma volume and the prevention of hypokalemia during diuresis are of far greater importance than the rapidity of sodium and water excretion.

Surgical Management of Ascites

Ascites can be controlled in the majority of cirrhotic patients by nonoperative means such as those enumerated above but there remain a few patients in whom the most stringent measures are unavailing and others for whom permanent control requires maintaining residence on a metabolic ward. Provided there is reasonable hepatic reserve, these patients may be considered for portacaval decompression. Prevailing surgical opinion^{20,77,78} reveals a preference for the side-to-side portacaval anastomosis because this operation preserves the portal vein as an outflow tract from the liver and reduces sinusoidal pressure while correcting splanchnic hypertension. The end-to-side anastomosis is believed to be less effective in relief of ascites because little decrease and often an increase in sinusoidal pressure may follow shunt of this type. No definitive explanation is available for occasional observations that end-to-side portacaval shunts cause the disappearance of ascites.

Burchell and associates⁷⁹ recently reported a 12 percent operative mortality in 63 patients with ascites treated by elective side-to-side portacaval

shunt. Fifty-six patients or 89 percent were subsequently clinically free of ascites. The variety of intraoperative hemodynamic determinations performed showed a lack of correlation with the subsequent clinical courses of these patients, once again emphasizing the difficulties in attempting to predict the effects of a given surgical procedure in a particular cirrhotic patient with portal hypertension.

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MEDICAL STAFF CONFERENCE

Progress in the Treatment of Advanced Breast Cancer

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. CARBONE:* The problem for presentation this morning** deals with the treatment of metastatic carcinoma of the breast. Dr. Robert Walter will present the patient.

DR. WALTER:† The patient is a 58-year-old Caucasian woman who was in good health until 1959 when she noticed a mass in the left breast. Left radical mastectomy was performed. Nine lymph nodes were found to be involved with carcinoma. Postoperative radiation was given to the left axilla. The patient then had no symptoms until September 1967 when a mass was found in the right breast. Right radical mastectomy was carried out, and no nodes were found to be involved with carcinoma.

In July 1968 an x-ray film of the chest demonstrated multiple small metastatic pulmonary nodules. A repeat film in August showed slight enlargement of these nodules, and stilbestrol therapy was started. Although the patient continued to feel well, in November 1968 progressive enlargement of the metastatic nodules was noted. Stilbestrol was discontinued and she was next treated with $7\beta,17\alpha$ -dimethyltestosterone, 100 mg twice daily by mouth. By February a significant

decrease in the size of the pulmonary metastatic lesions was observed (Figure 1), and this regression persisted on films taken in April 1969. The patient has noted no alopecia or facial hair growth. There has been no increased libido and no enlargement of the clitoris. During the first six weeks of therapy she experienced mild oiliness of the skin with a few comedones, but these have nearly disappeared. (This is the maximum degree of androgenicity we have seen in any patient on $7\beta,17\alpha$ -dimethyltestosterone; indeed, four of the eight patients who have been taking the drug long enough to be evaluated show no evidence of androgenic effect.) The patient continues to feel well at present.

Physical examination demonstrates only the evidence of bilateral radical mastectomies. She has no lymphadenopathy, cutaneous nodules, hepatomegaly, bone tenderness, or other evidence of metastatic disease.

Laboratory studies reveal the following to be within normal limits: hematocrit, leukocyte count, urinalysis, serum calcium level, and renal function studies. Serum glutamic oxaloacetic transaminase is 32 units (normal 5 to 40), and Bromsulphalein® retention is 8.5 percent at 45 minutes. A complete roentgen skeletal survey shows no abnormality.

*John V. Carbone, M.D., Professor of Medicine.

**30 April 1969.

†Robert M. Walter, M.D., Graduate Research Physician in the Department of Medicine.

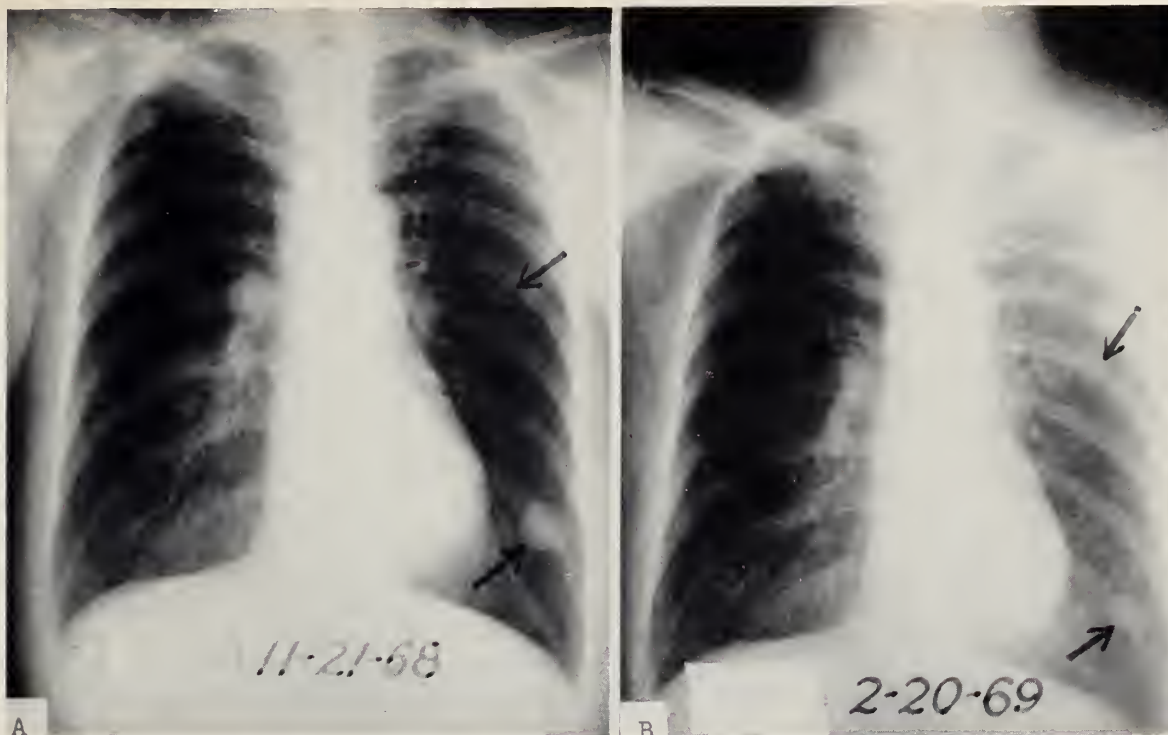


Figure 1.—Chest x-ray films (Case 4, Table 1). A. Before treatment with 7β , 17α -dimethyltestosterone, 200 mg daily. Note dense metastatic deposits in both lung fields (indicated by arrows). B. After three months of treatment. Note decrease in size of metastases.

DR. GORDAN: * Before telling you of some highly promising recent results we have observed in the treatment of women with advanced breast cancer, I think it important to review with you the magnitude of the problem, the difficulty in attempting to reconcile conflicting and overly enthusiastic reports in the literature, and to give you my view of the present status of endocrine therapy.

Breast cancer is an increasingly serious problem in this country. The incidence of this disease is rising; there are now 65,000 new cases and 28,000 deaths each year in the United States. Earlier figures from the Connecticut State Tumor Registry point out that 65 percent of women with breast cancer die of the disease.¹ These figures also show the chronicity of this disease, for it takes 15 years before the 65 percent figure is reached. From the clinical viewpoint, an equally striking fact is that during these 15 years women with metastatic breast cancer, unlike patients with other widespread malignant lesions, may look very well indeed and many show no cachexia or other disabling effects of malignancy even when riddled with metastatic lesions.

In the last few years it has been widely publicized that there has been no progress in the treatment of breast cancer during the last 30 years.² This gloomy conclusion is based on the fact that the number of deaths due to breast cancer per 100,000 female population has not changed. Not recognized in this isolated piece of information is the fact that the incidence of breast cancer is increasing in the United States, just as it is in England, Wales, and Scandinavia. Cutler and co-workers³ have pointed out that the increased incidence is not explained adequately by the increased longevity of the female population. In other words, there are more cases of breast cancer than expected for the number of women in the cancer age. Thus, the same number of deaths in the face of an increasing incidence indicates a better outcome. A very hopeful confirmation has come both from the Connecticut State Tumor Registry and from the California Registry. Cutler³ points out that in these two states the incidence is increasing even when adjusted for age, but, more exciting, the mortality is actually declining. This can only mean that in each individual case the odds of cure are greater than they were in the past. The survival rates also reflect this improvement. I sus-

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pect that the most important single factor responsible for saving lives and increasing survival is earlier detection.

Selection of Patients for Treatment

Since over 40 percent of patients with breast cancer go on to a disseminated stage and since the disease is so chronic, it is very important for every physician to know what can be achieved in improving the longevity and—even more important—the quality of life for these women. Unfortunately, the literature is chaotic and contradictory. In many reports regression rates from various procedures — administrative hormonal therapy, ablative endocrine surgery, or chemotherapy—are highly biased because of the way cases are selected for treatment and because varying arbitrary endpoints are taken for evaluation. It is now quite clear that there are at least three major variables which must be taken into account in selecting patients for experimental treatment: (1) The free interval—that is, the period from mastectomy to first recurrence, (2) the site of metastasis, and (3) the age of the patient. Goldenberg and co-workers⁴ have supplied valuable data indicating the importance of the free interval in patients who later received endocrine treatment for metastatic breast cancer. The shorter the free interval, the shorter the survival; and the longer the free interval, the greater the longevity. It is not, of course, surprising that slow growing cancers kill more slowly than rapidly growing tumors.

The second important variable is the site of metastasis. Escher's data from Memorial Hospital, New York⁵ show that of patients with metastasis to liver, lung or brain, 83 percent were dead in a year. If the tumor was confined to the breast, skin, and regional lymph nodes, the figure dropped to 27 percent. This, too, is not unexpected, indicating that patients whose tumors involve vital sites do less well than patients whose tumors choose sites that are not essential for life. Tumors confined to bone without visceral involvement have an intermediary effect. Failure to take these variables into account is exemplified by the study of the Therapeutic Trials Committee of the American Medical Association⁶ in which patients were given selectively estrogens or androgens for disseminated breast cancer. This was a pioneer study before all the present variables were known and has taught us a great deal of value in planning our present nationwide cooperative study. In the days when the American Medical Association study was car-

ried out, it was thought that young women responded better to androgens and older women to estrogens. Accordingly, the women treated with androgens averaged 20 years younger than those treated with estrogens. It is not, therefore, surprising that in this study estrogens came out superior to androgens, not because they are better, but because they were given in more favorable cases. It is well established that hormonal therapy is more effective in older than in younger women, and in the prospective comparison of testosterone propionate with stilbestrol, the present national Co-operative Breast Cancer Group obtained identical rates for the two compounds.^{7,8} Thus, almost anything can be proved about the efficacy of various compounds in the treatment of this disease, depending upon the kind of patient selected. This point is particularly applicable to endocrine ablative treatment, which has usually been reserved for patients without visceral disease and who, therefore, do better than patients with involvement of liver, lung or brain. For this reason, in the evaluation of an experimental compound it is essential that patients be randomized for the known variables so that similar groups receive the experimental treatment and a reference standard. Placebo treatment is not used for the control group since this would be unethical in patients with a disease which responds to hormonal therapy. Whenever possible, the double-blind technique should be used to avoid bias in comparisons.

Evaluation of Results

Just as selection is important, evaluation can be misleading, depending on the endpoints used. After careful evaluation of many indirect, non-specific effects such as urinary calcium excretion,⁹ weight, hematocrit, well-being and subjective response, it is apparent that evaluation must be based upon response of the tumor itself. The Co-operative Breast Cancer Group has developed the following criteria: A regression is identified only if measurable tumor masses shrink, osteolytic lesions recalcify, and there are no new lesions during the treatment period. Perhaps the most important requirement is that the regression must be agreed upon by two extramural examiners who review x-ray films, photographs, and measurements without knowing which patient received which compound.¹⁰ These are very stringent criteria and produce response rates less optimistic than those of more enthusiastic observers. It

should be noted that approximately twice as many women experience subjective improvement as show objective regressions.

Administrative hormonal therapy is given only to patients who are beyond surgical cure, whose disease is too widespread for x-ray palliation, and who are postmenopausal. Women who are still menstruating or who have had menstrual periods within one year have better regression rates from castration, induced either surgically or radiotherapeutically.

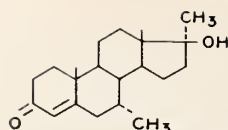
With these criteria the regression rates for testosterone propionate and for stilbestrol are identical at 21.5 percent.^{8,11} With either drug the response is best in the oldest women whose disease is confined to a local area. Osseous and soft tissue lesions respond equally well to either compound. Regressions last from six to forty-nine months, during which period patients not only show the objective changes previously described but usually have considerable subjective relief. I might add that our clinic no longer uses testosterone propionate, since as good or better results can be obtained with nonmasculinizing compounds. In my view, the virilization produced by testosterone propionate makes it a cruel treatment even though it is effective. Since I consider androgenicity sufficiently undesirable to contraindicate using an effective agent, it is not difficult to imagine how I feel about more drastic procedures such as the early use of toxic chemotherapeutic agents or ablative procedures.

It is now well established that patients who respond to hormonal treatment survive longer than those who do not. As I mentioned, the quality of life is greatly improved in these responders. We now have a fairly large number of compounds which give rates equal or superior to those produced by testosterone or stilbestrol. Many of these are more advantageous from the standpoint of fewer undesirable effects. We now have firm data on the response rates obtained with an array of compounds which have been tried by the Cooperative Breast Cancer Group. I would like to reemphasize that these results are obtained in patients who are beyond surgical cure, whose disease is too widespread for roentgen palliation, and in whom the disease is objectively progressing. One of the first compounds evaluated in this institution was fluoxymesterone [Halotestin® (Upjohn), Ultandren® (Ciba), Ora-Testryl® (Squibb)]. This compound had been widely touted in an earlier

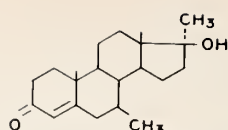
uncontrolled study, without extramural reviewers, as producing 53 percent regressions.¹² The figure from the University of California study was 14 percent¹³ and the nationwide figure 15 percent.¹¹ Fluoxymesterone, however, has several advantages. It is effective by mouth and produces little visible androgenicity, with none of the increase in libido which can be such a distressing effect of androgens in older women.

Compounds with Antitumor Effects

We now have several compounds with antitumor efficacy similar to that of testosterone or stilbestrol. One of these, Δ^1 -testololactone, is a most remarkable compound.¹¹ It has neither estrogenic nor androgenic activity, is effective by mouth, and is completely nontoxic.¹⁴ It has been remarked facetiously that it cannot be a hormone since it has no "side effects." In the same category are two androgen derivatives: 2α -methyl-dihydro-testosterone, which is an effective agent when given by the oral route, and its propionate, which is given by intramuscular injection. The latter is commercially available as Drolban® (Lilly). It also has the advantage of being only a very mild androgen and, therefore, is more acceptable than testosterone propionate.¹⁵ The cooperative study has given valuable data on the therapeutic index, the ratio of desirable to undesirable effects. This is well exemplified by Broxoron® (9α -bromo-11-oxo-progesterone). This compound is nearly as effective an antitumor agent as testosterone propionate.¹⁶ It has no androgenic or estrogenic activity, but unfortunately it is a very potent salt retainer; severe edema develops in almost all patients given antitumor doses. Another compound with antitumor activity similar to that of testosterone is 17α -methyl-19-nortestosterone. When taken in antitumor doses, the well-known hepatotoxic effect of the 17α -alkyl radical makes this an unacceptable compound. It uniformly produces Bromsulphalein® retention and often jaundice.¹⁷ Another compound in this category, $7\alpha,17\alpha$ -dimethyltestosterone, was selected because animal studies showed that the 7α -methyl group greatly increases muscle building or anabolic activity. This compound is as effective as testosterone propionate but is also a very potent androgen and often causes Bromsulphalein® retention.¹⁸ Possibly because of the smaller doses used, it has not caused jaundice or other evidence of hepatocellular damage. I call attention to this compound because I



7 α ,17 α DIMETHYLTESTOSTERONE



7 β ,17 α DIMETHYLTESTOSTERONE

Chart 1.—Formulas of 7 α ,17 α -dimethyltestosterone and 7 β ,17 α -dimethyltestosterone. Difference is steric configuration of methyl group attached to carbon 7.

will discuss below the 7 β epimer, that is, 7 β ,17 α -dimethyltestosterone (Chart 1).

I think it is clear from what has been said that there is great need to improve the treatment of women with advanced breast cancer. For 20 years we have had in this institution an Advanced Breast Tumor Clinic which includes surgeons, radiologists, pathologists, endocrinologists and chemotherapists. Since 1957 we have been participating in the nationwide Cooperative Breast Cancer Group sponsored by the National Institutes of Health. One of the major pioneer efforts of our clinic is secondary hormonal therapy. As indicated above, only 20 to 35 percent of patients show objective regressions with the first hormonal maneuver; hence the vast majority of patients require a change of treatment. Even those who respond will inexorably relapse, at which time a secondary treatment is indicated.

One method of treatment is to withdraw hormonal therapy and look for rebound regression. The careful studies of Kaufman and Escher¹⁹ show that this maneuver is indeed worthwhile but only in patients who have had a favorable response to

estrogen therapy. The response rate in estrogen failures is only approximately 3 percent, and for patients previously treated with androgens it is only approximately 2 percent. Until recently it was thought that if the patient failed to respond to estrogen, she should then be given a trial of androgen, and vice versa. Our studies and the studies of the 31 institutions then participating in the cooperative study indicated that these treatments give a very low order of regression—4 percent for estrogens, 9 percent for androgens, and 5 percent for corticoids.^{20,21} The weak androgen Drolban® was as effective for secondary as for primary hormonal therapy, producing 19 percent regressions.

Until recently the most exciting development was the study in which we compared the efficacy of hypophysectomy and of replacement therapy in a randomized series of unselected patients with advanced breast cancer. Hypophysectomy plus replacement with cortisol, 30 mg daily, and triiodothyronine, 50 mcg daily, produced only 11 percent regressions. Replacement therapy alone produced 22 percent regressions, was far easier on the patient, and in this dose caused no adverse effects whatsoever.

Sequential therapy, therefore, usually consists of castration (if the patient is premenopausal), and first trial of hormonal therapy, secondary hormonal therapy, and finally chemotherapy, rarely followed by endocrine ablative procedures for those few patients who have previously responded to castration and whose disease is progressing and no longer responding to administrative therapy.

TABLE 1.—Phase I Study of 7 β ,17 α -Dimethyltestosterone as Late Hormonal Therapy in Advanced Breast Cancer (3.4 mg/kg/day by mouth for 6 weeks to 9 months)

Patient	Age	Mastectomy	Site of Metastasis	Previous Modality	Treatment Response	7 β ,17 α -Dimethyltestosterone	
						Dose mg/day	Response
1.	53	1962	Osseous	Castration	Regression	250	Osseous regression
2.	63	1966	Osseous	Cortisol	Regression	250	Osseous regression
				Cortisol + Triiodothyronine	Failure		
3.	63	1963	Osseous	Stilbestrol	Failure	250	Osseous regression
4.	57	1959, 1967	Visceral: Lung	Stilbestrol	Failure	200	Pulmonary regression
5.	58	1966	Visceral: Right lower quadrant mass	Ethinyl estradiol	Failure	200	Visceral and osseous regression
			Osseous	Delatestryl®	Failure		
6.	54	1954, 1957	Visceral: Pleural	Chlorambucil	Failure	200	Osseous regression
			Osseous	Stilbestrol	Failure		
7.	53	1963	Osseous	Δ^1 -Testololactone	Failure	150	Osseous regression (Unreviewed)
				Testosterone propionate	Failure		
8.	52	1961	Osseous	5-Fluorouracil	Failure	300	Osseous regression (Unreviewed)
				Cortisol + Triiodothyronine	Failure		

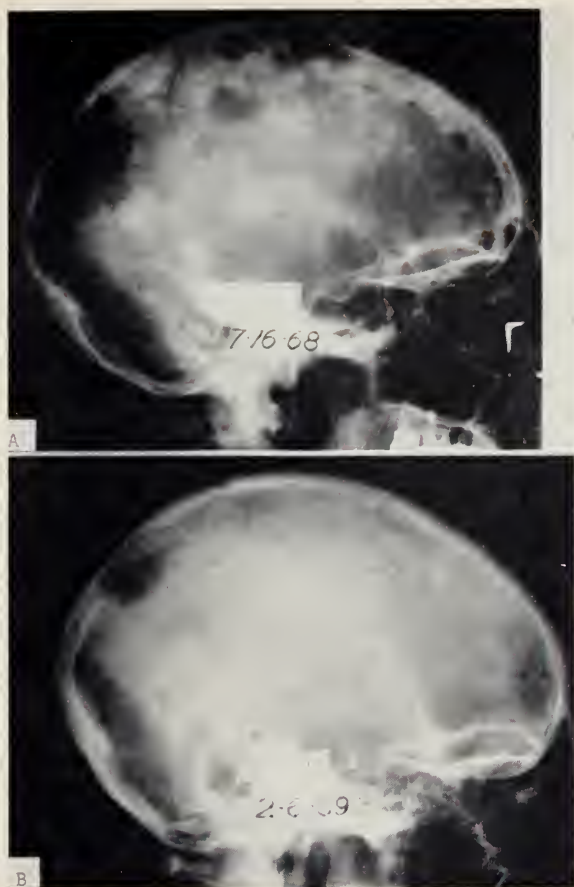


Figure 2.—Skull films (Case 1, Table 1). A. Before treatment with $7\beta,17\alpha$ -dimethyltestosterone, 250 mg daily. Note widespread osteolytic lesions. B. After seven months of treatment. Note decrease in size of lesions, recalcification, and replacement with normal-appearing bone.

This sequence results in objective regressions in almost 50 percent of all patients with advanced breast cancer.

Experience with $7\beta,17\alpha$ -Dimethyltestosterone

Recently we have been performing Phase I studies* in patients who have progressive disease which is not responding to primary or secondary hormonal therapy. Phase I studies consist of administration of a compound (usually selected on the basis of animal test data) to a small group of patients to determine its effectiveness and how well it is tolerated. Because $7\beta,17\alpha$ -dimethyltestosterone (Chart 1) has little endocrine or, indeed, any activity in animal tests, we elected to try it in a Phase I study (Table 1). This compound was synthesized by Dr. John C. Babcock of the

Upjohn Company as a byproduct of $7\alpha,17\alpha$ -dimethyltestosterone (Myagen®, Upjohn), the androgenic, anabolic compound with antitumor activity like that of testosterone propionate referred to above.

The first patient was given this compound last July. She is a 53-year-old woman who had a radical mastectomy in 1962 and a free interval of 32 months before the development of osseous metastatic disease. She had bilateral oophorectomy in 1965 and in April 1967 was treated with cortisol for local progression. In July 1968 because of rapidly progressing, widespread osseous metastasis she was given $7\beta,17\alpha$ -dimethyltestosterone, 250 mg daily. Figure 2 demonstrates the striking recalcification of osteolytic metastases in the skull; there was a similar good effect in the pelvis. She had no significant virilization and no hepatic toxicity as evidenced by serum alkaline phosphatase, serum glutamic oxaloacetic transaminase levels, or Bromsulphalein® retention.

A similar result was obtained in a 63-year-old woman (Case 2, Table 1) who had mastectomy in 1966 and was found to have metastasis to bone 14 months later. She was treated first with radiation, then with cortisol plus triiodothyronine, and finally with stilbestrol, without obtaining regression. In September 1968 she was given $7\beta,17\alpha$ -dimethyltestosterone with prompt recalcification of osteolytic metastases. She, too, had no significant virilization or hepatic toxicity. Unfortunately, she had widespread atherosclerosis which had previously caused a myocardial infarction. At the end of February 1969 she had a sudden mesenteric thrombosis and died.

Figure 3 shows the results in a 63-year-old woman (Case 3, Table 1) who had a radical mastectomy in 1963. She was found to have osseous metastatic disease three and a half years later, for which she received x-ray treatment. The disease did not respond to stilbestrol or to ethinyl estradiol. In November 1968 she was given $7\beta,17\alpha$ -dimethyltestosterone. The skull lesions rapidly recalcified, and there was also improvement in osteolytic lesions in the pelvis. She is still receiving the agent and has no significant androgenicity or any evidence of hepatic toxicity.

Our next patient was a 58-year-old woman (Case 4, Table 1) who had a mastectomy in 1966. Two years later she had widespread osseous metastasis and a pathologic fracture of the right hip treated by x-ray therapy. The disease did not re-

*Study aided by U.S.P.H.S. grant CA-03489.

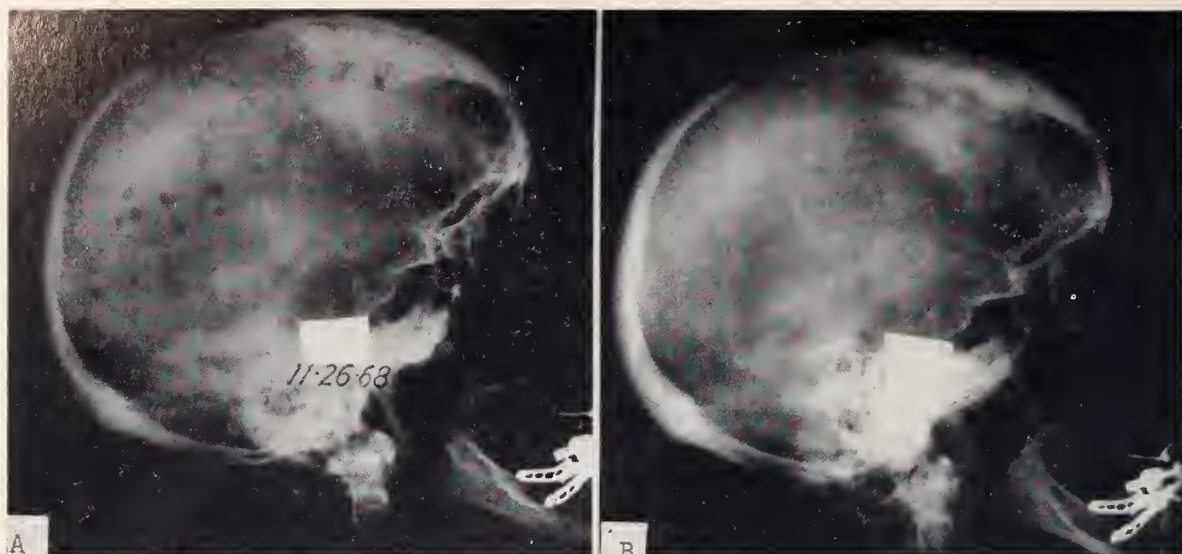


Figure 3.—Skull films (Case 3, Table 1). A. Before treatment with $7\beta,17\alpha$ -dimethyltestosterone, 250 mg daily. Note multiple, punched-out osteolytic metastases. B. After five months of treatment. Note recalcification of lesions.

spond to a long-acting testosterone preparation or to chlorambucil. In July 1968 a rock-hard mass approximately 7 cm in diameter was felt in the right lower quadrant. Because of rapid osseous progression $7\beta,17\alpha$ -dimethyltestosterone was given. The abdominal mass was reduced to half its diameter in six weeks and disappeared at three months. Osteolytic lesions in the skull, pelvis and femurs recalcified.

Our sixth patient (Case 6, Table 1) had unusually rapid healing of osseous metastatic disease with this agent. She was a 54-year-old woman who had a right radical mastectomy in 1954 and a left radical mastectomy in 1957. In 1968 she was found to have a large supraclavicular mass and a malignant pleural effusion and was given stilbestrol without effect. Because of progression of the osseous lesions, in January 1969 she was given $7\beta,17\alpha$ -dimethyltestosterone. X-ray films showed rapid healing of an osteolytic lesion in the rib in only six weeks. In my experience this is an unusually prompt and gratifying response.

This series of six patients was reviewed by two extramural examiners one month ago. All six patients who had received the agent for more than two weeks showed objective regressions. Since that time two further patients have been treated long enough to show what we consider unequivocal regressions, although these two have not yet been reviewed. Because of these unprecedented good results in highly unfavorable cases, the National Cancer Institute has funded the synthesis of a

larger amount of compound, and the Upjohn Company has instituted a crash program to produce the material. It should be emphasized that although these results are highly promising, they are still preliminary in that the number of patients is still small. It is our hope to expand this series as rapidly as possible now that we know more material will be forthcoming.

In conclusion, the treatment of patients with breast cancer has clearly been improved. The decline in mortality despite increasing incidence definitely indicates better early treatment. Even when the disease is disseminated, treatment can be greatly improved by sequential hormonal administration. It is now possible to produce regressions in nearly half our patients during the first, second or third treatment. We now have enough firm information to know which patients are likely to respond to which treatment, to tailor the treatment to the individual patient, and to obtain more regressions with fewer adverse effects, hormonal or otherwise. The most promising data I have seen in my 20 years of participation in this study are those presented to you today with $7\beta,17\alpha$ -dimethyltestosterone, a nontoxic, nonvirilizing testosterone derivative which has produced regressions in all of eight women with advancing, hormone-resistant metastatic breast cancer treated for more than two weeks. I hope we will be able to give an equally favorable report when we have more experience with a larger number of patients.

DR. CARBONE: Thank you very much, Dr. Gordan.

This, indeed, is a most exciting development. Are there any questions for Dr. Gordan?

QUESTION: How long would you maintain therapy?

DR. GORDAN: The longest treatment so far has been nine months, and we plan to continue treatment as long as regression persists. In the event of relapse, we will then try the effect of withdrawal.

DR. WILLIAMS:* Do you think there is any difference in the response of osseous metastasis when compared with visceral metastasis?

DR. GORDAN: We have only eight cases so far. Three of the patients have soft tissue lesions, in one case a rock-hard mass 7 cm in diameter in the right lower quadrant. After six weeks of therapy this mass had decreased in size, and in three months it was gone. Thus, in three patients with soft tissue lesions and in seven patients with osseous disease, we now have objective regressions by the group criteria.

*Hibbard E. Williams, M.D., Assistant Professor of Medicine.

ADDENDUM (June 20)

The objective regression in our first patient (Case 1, Table 1) lasted nine months. Osseous and cutaneous lesions reappeared in April 1969, accompanied by hypercalcemia. No rebound regression was observed in six weeks after withdrawal of $7\beta,17\alpha$ -dimethyltestosterone. This recurrence indicates that the compound, like other steroidal antitumor agents, is not a cancer cure, but rather produces rapid objective and subjective improvement in many highly unfavorable, hormone-resistant cases of advanced breast cancer.

Since the original six reviewed regressions, seven additional patients have been treated long enough for our evaluation. (These have not yet been reviewed by extramural examiners.) One of these died in the third week of treatment and is classified as a failure of treatment. Of the other six patients, one has shown a definite regression of multiple pulmonary metastatic lesions and two have shown regression of cutaneous nodules. The remaining three, who have all experienced substantial subjective improvement, show what we believe to be early regression of osseous metastatic disease. All of these seven additional patients had previously not responded to hormonal therapy or chemotherapy. Additional patients have been entered on the study, but for too short a time for evaluation at present.

GENERIC AND TRADE NAMES OF DRUGS

Sulfobromophthalein sodium—*Bromsulphalein*®
Fluoxymesterone — *Halotestin*®, *Ora-Testryl*®, *Ultandren*®
Dromostanolone (2α -methyl-dihydrotestosterone propionate)—*Drolban*®
 9α -bromo-11-oxoprogesterone—*Broxoron*®
Bolasterone ($7\alpha,17\alpha$ -dimethyltestosterone)—*Myagen*®
Testosterone enanthate—*Delatestryl*®

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Special Article

The Golden State Medical Association

The California Chapter of the National Medical Association

JULIUS W. HILL, M.D., *Los Angeles*

IN CALIFORNIA the Golden State Medical Association, which is the statewide constituent society of the National Medical Association, is less well known than some of the smaller component societies that it encompasses in this state. For example, in Southern California the Charles R. Drew Medical Society, made up predominantly of the physicians in the Los Angeles County region, is well known in medical circles throughout the state. The John Hale Medical Society of San Francisco is well known in the Bay Area. It is that society which next month will host the National Medical Association's annual meeting, to be held in San Francisco. The younger component societies in California, namely the San Joaquin Valley Medical Society, the Sinkler-Miller Medical Society of Oakland, the Richmond Medical Society of Richmond, California, and the San Diego Medical Society, are the most recent organizations of the National Medical Association. They are well known in their areas. What the majority of people in California are not aware of is that all these satellite organizations are components and operate under the charter of a constituent society of the National Medical Association, namely the Golden State Medical Association.

Submitted 12 June 1969.

Dr. Hill is President of the Golden State Medical Association and President-Elect of the National Medical Association, to be installed as President at its annual meeting to be held in San Francisco, August 10-14, 1969.

Reprint requests to: Golden State Medical Association, 1828 South Western Avenue, Los Angeles 90006.

The National Medical Association (NMA) is an organization founded in 1895 in Atlanta, Georgia, by a small group of Negro physicians, dentists and pharmacists who during that era found it impossible even to be considered for membership in any other medical, dental or pharmaceutical society.

The *raison d'être* for NMA was that the pattern of racial separation and discrimination was so prevalent in this country that the Negro physician whose training in those days was limited to two Negro medical schools, namely, Meharry Medical College, Nashville, Tennessee, and the Howard University College of Medicine in Washington, D.C., found that it was almost impossible after their medical training to receive internships or residencies, or even to practice medicine in accredited and many non-accredited hospitals. The plight of the Negro physician at the time of the founding of the National Medical Association was such throughout the nation that he was unable to attend scientific sessions of any sort designed for increasing the scientific knowledge of the physician throughout our nation. The National Medical Association's reason for being is still with us in this year of our Lord, 1969.

One of the past presidents of the National Medical Association, Dr. Leonadis H. Berry, in an article published to be read at a meeting of the AMA and NMA liaison committee on 27 September 1965, stated:

"Since the turn of the century 65 years ago, there have been efforts on the part of the officers of the NMA to remove the principal cause or reason for the origin and development of the NMA, namely discriminatory practices against qualified physicians because of race. For at least 25 years, there has been utilized off and on the concept of liaison meetings between the two organizations as to what the AMA may or should do towards eliminating the barrier of basic memberships in the AMA and its constituent and component societies. This practice has been carried out by constitutional requirements in the South and some border states, and by tactful permissibility on the part of the general organization. To a lesser degree, these liaison groups have been concerned with discriminatory practices in medical education, hospital appointments, discriminatory practices against Negro patients, and the perpetuation of the segregated image in medicine."

The National Medical Association has been active throughout the 74 years of its existence in the cause of the best health care for all Americans without discrimination of any kind. The NMA has also traditionally lent its own strength to campaigns toward common goals with other organizations. The passage of the Civil Rights Act of 1964 came only after years of accumulative collaborative efforts by hundreds of organizations and individuals, spearheaded always by the NAACP with the NMA doing its part both as an organization and through efforts of individual members. Since the civil rights field now swarms with leaders, hitherto unknown, be it understood that the NMA has never abandoned or relinquished its experience and activity in this sphere of its interest. All who are members of the NMA or hold office in the organization have been expected to enhance and expand its effectiveness. The National Medical Association currently has duly appointed committees, charged with furthering the implementation of Title VI of the Civil Rights Act with respect to health. The National Medical Association was the only national organization of physicians to declare for Medicare, now the law of the land, a declaration twice reaffirmed. The National Medical Association is known as the liberal wing of the medical profession.

Membership Not Limited to Negroes

Membership in the NMA is not limited to members of the Negro race. The NMA has always welcomed members of the medical profession from

other racial groups. Recently the NMA suspended one of its chapters in the New York area for refusing to accept a Caucasian member to its roster, and upon investigation it was found that one of the officers of the New York chapter had blackballed the Caucasian physician for very personal reasons. The New York society made it its business to investigate this irregularity and threatened the member barring the Caucasian's admission with expulsion. The Caucasian physician is at present an officer in the New York chapter. The NMA is renowned for disciplinary action toward its component and constituent societies.

Admission to the National Medical Association is not through coercion. That is to say, membership in the NMA is not required in order to become a member of a hospital staff or procure malpractice insurance, nor is membership in the NMA essential if one is to advance in the medical profession. Membership is purely voluntary without restriction as to race, creed or color; the major requirements are that the prospective member have an M.D. degree and a license to practice medicine in the state or area in which he resides, that he be of good moral character and have a strong determination to help alleviate human suffering.

The Golden State Medical Society embodies all of the above principles and since its organization in 1961 has been nurtured and carefully directed by the Charles R. Drew Medical Society of Los Angeles.

Background of the Drew Society

It was necessary for the Charles R. Drew Medical Society to organize the Golden State Medical Association in order that the Drew society could qualify for membership in the NMA. The Drew society was formed in Los Angeles. It began as a physicians' and surgeons' literary and social club. The purpose at that time was two-fold: one, that there was a need for local physicians to be organized to discuss and act on problems peculiar to men of medicine only, and second, to have scientific discussions and to keep abreast of the latest scientific information. The founding meeting was held 11 August 1950. The organization took its name in salute to the late Charles R. Drew, an illustrious physician and surgeon, an alumnus of Howard University, who died 1 April 1950. Dr. Drew is best remembered for his work in the founding of an establishment of blood plasma banks in Great Britain and in the United States

during World War II. Dr. Drew was also professor of surgery at Howard University in Washington, D.C.

To tell the story of the Golden State Medical Association, one must tell the story of the Charles R. Drew Medical Society, the story of the John Hale Medical Society of San Francisco, and the story of members of the National Medical Association elsewhere throughout the State of California where the physician population of NMA members is too small for chapter organization. The Golden State Medical Association hails every victory made by its membership toward bettering the condition for the alleviation of human suffering and contributing to the dignity of mankind. The Charles R. Drew Medical Society fought valiantly along with the administrative officers of the County of Los Angeles in their effort to procure approval of the Martin Luther King, Jr., County Hospital facility now under construction in the Los Angeles area. The Charles R. Drew Medical Society spearheaded, initiated and chartered the Charles R. Drew's Post Graduate Medical School, which will be closely affiliated with the Martin Luther King, Jr., County Hospital. The Charles R. Drew Medical Society worked closely with and took a meaningful position in the establishment of the University of Southern California Watts Health Clinic, now operating in the City of Los Angeles.

The John Hale Medical Society of San Francisco has a record in its brief period of three years of existence which causes its sister chapter in Southern California at times to blush with pride. There are approximately 6,000 Negro physicians in the United States, of which 85 percent are graduates of either Howard University College of Medicine or of Meharry Medical College. The other 15 percent have graduated from other medical schools which have been enlightened enough to admit scholars of ebony hue. More than 10 percent of all of the Negro physicians in the United States reside in California. The Golden State Medical Association, one of the youngest constituent societies in the NMA, is fast becoming one of the most outstanding. It has progressed with praise from the membership and other societies throughout the nation.

Talent Recruitment

The National Medical Association is not a wealthy organization, nor is the Golden State Medical Association. The component societies that the Golden State Medical Association comprises

are also not endowed with pecuniary abundance, yet projects and programs deemed essential to the continued progress of the organization are almost always provided for. Some of the most important programs at the present time being sponsored by the organization are the talent recruitment program which was begun approximately five years ago, even before such programs became a matter of national interest. This program sponsored and initiated by the NMA is one whereby medical and paramedical talent is searched for and, when found, encouraged to seek medical and paramedical training. Another major task of the NMA, the Golden State Medical Association and its component societies, as well as those throughout the nation, is that of encouraging the major medical and paramedical institutions throughout the nation to accept more minority students to their rosters. The NMA pioneered this phase of scholar recruitment. The dearth of Negro medical personnel, especially physicians, is of greater concern to the NMA than possibly to any other organization claiming interest in this matter. This statistic as compiled by the NMA pertaining to the ratio of minority physicians, especially Negro physicians, in accordance with the American population indicates that one out of every 7,000 Negroes can aspire to become a physician, while for whites the number is one out of every 632.

The National Medical Association has provided a scholarship fund which throughout the years has paid all or part of tuition cost for deserving scholars seeking training in the medical profession. However the scholarships unfortunately have been limited only to those of very superior scholastic standing. The association will probably alter its requirement for scholarships, just as is being done throughout the nation in lowering medical school requirements for underprivileged and/or socio-economically deprived students.

One of the most important concerns of the Golden State Medical Association at present is to have its personnel more recognized as a part of the California medical scene. The members of the Golden State Medical Association are eager to extend the hand of friendship and cooperation as well as the feeling of brotherhood among all the members of our great profession. Although not affluent or large of membership, the Golden State Medical Association prides itself on the quality of its membership. It, as well as the National Medical Association and the component societies,

encourage and assist the members to maintain the highest standards of the medical profession.

Embodied in the structure of the Golden State Medical Association are board-eligible and qualified specialists in every field of medicine, although not in the quantity desired. From the general practitioner to the superspecialist, the Golden State Society stands ready to serve the California community. A step in the right direction was the recent endorsement by the Council of the California Medical Association and the membership of the Golden State Medical Association of the formation of a liaison committee for the purpose of bridging gaps that might exist between the black professional and his white brother. The members of the Golden State Medical Association stand ready to serve and to cooperate with every endeavor which promotes the best health care for our California citizens, regardless of race, creed,

color and socio-economic position.

The Golden State Medical Association advocates, as was previously mentioned, a spirit of cooperation and respect with a strong bond of friendship encouraged by the common goal of service to humanity.

One of the most important factors of the membership of the Golden State Medical Association is that almost 100 percent of the membership are also members of the American Medical Association, the California Medical Association and the local county societies throughout the state. There is a little dichotomy existing in our state and it is felt that this dichotomy is due solely to the fact that there has not been enough fraternization and friendship exemplified. One can appreciate his fellowman only if he knows him. One cannot know his fellowman if he remains aloof and apart from him.

RENAL LESIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

"There are several [renal] lesions accompanying systemic lupus [erythematosus], and they vary in their need for being treated. There is what has been called a glomerulitis, which is a lesion that is characterized by red cells in the urine, perhaps a small amount of protein, and rather minimal inflammation of the glomerulus. These, in general, do fairly well. Then there is a more intense lesion that has passed under the term of systemic lupus glomerulonephritis. This involves the glomeruli severely — with proliferation, ultimately scarring, thrombi, and invasion with leukocytes, etc.; and in addition, it involves the tubules and the interstitium. This is indeed a very serious lesion. Then finally one can have a straight so-called membranous lesion with systemic lupus. These tend to do fairly well. I think that it's important to point out that as one looks at patients with lupus lesions, about 25 to 30 percent will develop a nephrotic syndrome. I think this is always an indication for treatment."

—JAMES HOPPER, JR., M.D., San Francisco
Extracted from *Audio-Digest Internal Medicine*, Vol. 15, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

The Specter of Malpractice

GEOFFREY E. LINBURN, M.D., *Denver*

THE SPECTER OF MALPRACTICE haunts many physicians. To these physicians the threat of being held publicly accountable for their professional actions arouses considerable anxiety. In an effort to allay this anxiety they have sought culprits whom they can blame for their distress. By this path they have been led to believe in a legal conspiracy. In this conspiracy, they believe, opportunistic patients bring suits against the innocent doctor, mercenary lawyers encourage such suits, naive juries sympathetic to the injured patient bring in large verdicts, and courts continue to extend rulings prejudicial to the doctor.

Defensive Medicine

Physicians' defense against this conjured threat has taken several forms. One form of defense has been the practice of defensive medicine. From fear of possible litigation, valuable procedures such as caudal anesthesia have been tabooed while over-diagnosis with the excessive use of x-rays and laboratory tests has become commonplace. These policies have deprived patients of valuable medical procedures and have imposed unnecessary expenses and hazards.

The "Conspiracy of Silence"

The only evidence that can decide a case of malpractice is expert evidence: that is, the evidence of other doctors; and every doctor will allow a colleague to decimate a whole countryside sooner than violate the bond of professional etiquette by giving

him away . . . He is not sure enough of his own opinion to ruin another man by it. . . . I do not blame him: I should do the same myself. But the effect of this state of things is to make the medical profession a *conspiracy* to hide its own shortcoming. [Emphasis added]

—G. B. Shaw, *The Doctor's Dilemma*¹

These observations indulgently expressed by George Bernard Shaw more than a half century ago were more recently transformed by the well-known plaintiff lawyer, Melvin Belli, into the more bellicose designation of a "conspiracy of silence."² This heated phrase emerged from the kiln of malpractice litigation in which plaintiff lawyers were frequently frustrated in their attempts to obtain medical testimony. To a 1957 *Stanford Law Review* questionnaire, 16 of 21 plaintiff lawyers in California responded that obtaining medical testimony for their clients was almost impossible to outright impossible.³

The reluctance of physicians to provide testimony establishing a standard of care has also been widely recognized by the courts. In *Salgo v. Stanford* (Cal., 1957), for example, Justice Bray observed that "... gradually the courts awoke to the so-called 'conspiracy of silence.' No matter how lacking in skill or how negligent the medical man might be, it was almost impossible to get other medical men to testify adversely to him in litigation based on his alleged negligence."⁴

Since in most malpractice cases the expert testimony of a physician is required to establish the standard of care by which the defendant physician's conduct is to be judged, the refusal by physicians to provide such testimony may lead to the dismissal of the plaintiff's suit for want of sufficient evidence. The patient is thereby deprived of his legal right to damages for negligent injuries.

Submitted 12 May 1969.

At the time he submitted this paper for publication, the author was a fifth-year student at Stanford University School of Medicine. He received his doctorate in medicine in June of this year and is at present interning at Denver General Hospital in Denver.

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While the California courts have not directly repudiated this tactic, they have tried to help the plaintiff out of his predicament by stretching old rules of evidence and formulating new ones. In California, for example, drug company brochures are admissible as evidence pertinent to establishing the standard of care for drug administration.⁴ The California courts have also liberalized the qualifications of an expert witness. Originally, negligence of a physician was measured against the reasonable standard of care practiced in the physician's community and established by the testimony of local physicians. But since physicians from the same community as the defendant are less likely to testify against the defendant than physicians from another community, the courts have attempted to liberalize the qualifications of an expert witness to permit physicians from other communities to testify. In *Sinz v. Owens* (Cal., 1949), for example, the California Supreme Court qualified an expert witness from another community on the grounds that he was familiar with the standards required of physicians "under similar circumstances" to those applying to the defendant.⁵ In the event that no other physician can be obtained to testify, the defendant physician himself may be used as an adverse expert witness by the plaintiff lawyer to establish a standard of care.⁶

The most significant development in the attempt by the California courts to circumvent the "conspiracy of silence," however, has been to extend the application of the doctrine of *res ipsa loquitur*. Originally intended as a rule of circumstantial evidence ("the thing speaks for itself"), the doctrine has been extended in some circumstances to impose an obligation on physician defendants to advance evidence of non-negligence. In the usual negligence case, the burden of proof rests with the plaintiff who presses charges. But since malpractice litigation generally requires the testimony of physicians establishing a standard of care by which the case can be judged, the difficulty in obtaining such testimony provoked the courts into extending the application of *res ipsa loquitur* to impose some burden on the medical profession to provide such testimony. The intent behind so applying the doctrine has been to permit the plaintiff patient his day in court. The danger in so applying the doctrine to malpractice cases has been to unjustly imply the guilt of the physician.

Over the past decade the California Medical Association has tried to make available expert wit-

nesses to plaintiff lawyers through the establishment of medical expert panels.^{7,8} Although these efforts have helped to make medical testimony more available to the plaintiff, plaintiff lawyers continue to complain that adequate medical testimony is still difficult to obtain.

Speak No Evil

A final form of defense against the specter of malpractice has been the frequent, tacit agreement among physicians not to hold one another accountable for a standard of care. Local medical societies, for example, have made little effort to enforce such a standard. A survey by the American Medical Association of 1,100 county medical societies revealed that in a period of two years only 21 physicians were expelled. Of these 21, only four were expelled for offenses against patients.⁹

Certified hospitals are one area in which the medical profession has made significant efforts to scrutinize its own practices. Surveillance of the professional staff is accomplished by review of qualifications on admission to staff, restriction of privileges, and record and tissue review committees. However, even in accredited hospitals the practices of most physicians on non-surgical services is reviewed very casually; little or no work of any kind is reviewed in non-accredited hospitals; and office practice is not reviewed at all.

By largely abdicating the responsibility for maintaining a standard of care, physicians have left this territory for the legal profession to regulate.

The Inner War

In attempting to defend themselves against what they appear to believe to be a "legal conspiracy," physicians have engaged in a battle which has damaged both medical practices and legal processes. Meanwhile the specter of malpractice looms larger than ever.

The Illusory "Conspiracy"

Although examples can be found to support the belief in a legal conspiracy that significantly harms the innocent physician, the weight of evidence is contradictory. Only in the exceptional case is the physician unjustly convicted of malpractice.¹⁰ And even more exceptional is the conviction which significantly harms the physician.¹¹ Malpractice insurance is available to practically every physician¹²; and the high cost of such insurance is generally defrayed by the public by increased medical fees.

The only well-documented finding lending support to the belief in a legal conspiracy is the high proportion of malpractice claims that have little medical merit. In a study of the causes of malpractice claims in California, Richard Blum observed that not more than 10 percent of malpractice claims are based on actual malpractice.¹³

But while physicians have been understandably indignant at having to publicly discredit unmerited accusations, this provocation, as with the other reasons usually cited, does not adequately account for their defensive behavior. In the first place, there is little evidence to suggest that doctors distinguish between those cases with and those without medical merit in reaching their decision as to whether or not they will testify—most physicians will not testify regardless of the medical merits of the case. Furthermore, the practice of defensive medicine seems to be conditioned more by a general desire to avoid any malpractice claim than by a discriminant concern to frustrate unmerited claims.

Although the possibility of a malpractice suit is real, the "legal conspiracy" which many physicians envision is a distortion of the actual threat. The risk of malpractice admittedly is sufficient to warrant a physician's carrying malpractice insurance. But the risk realistically recognized by carrying such insurance is of a different order from that sufficient to substantiate the belief in a legal conspiracy which has led to the practice of defensive medicine and to the so-called "conspiracy of silence."

The Need for an Illusion

Although the belief in a legal conspiracy has little objective validity, compelling reasons exist to explain its subjective necessity. "In the United States today the physician typically enjoys to an unusual degree good income, social prestige, and the esteem of the community. Little in his training or environment conditions him for criticism, deprecation, or attack."¹⁴ Medicine has attracted many persons who thrive in this aura of respect and come to depend on it. In turn, they often come to half believe in the public's unrealistic expectations of their dedication and wisdom on which this respect is based. Such physicians have particular difficulty comprehending and tolerating the discrepancy between the respect to which they are accustomed and the indignity of a malpractice suit. Their inability to acknowledge their need for this

uncritical respect leads them to envision a legal conspiracy. By then acting as if they were defending themselves against this envisioned conspiracy, they are able to defend their self-esteem without having to acknowledge this need.

While the need for uncritical respect varies for different physicians, it tends to be greatest in those most vehemently opposed to and most commonly involved in malpractice litigation. In Blum's study on the causes of malpractice,¹³ it was found that doctors involved in multiple suits—they are termed "suit-prone"—have personality profiles that differ significantly from those of doctors involved in one or no suits. The suit-prone doctor is more likely to be immature, to have low self-esteem, to have difficulty handling emotional problems, to dislike his patients yet want them to be dependent and grateful, to act as if he were infallible—preferring not to have consultants and tending to blame others for his own mistakes, and to be defensive. Such a doctor, according to this study, is more likely to antagonize his patient who, in turn, because of the taboo against expressing anger in a doctor-patient relationship, may express his anger in the more acceptable form of a malpractice suit. For such a doctor the need to believe in a legal conspiracy is particularly compelling.

Created largely as a defense to protect physicians' threatened self-esteem, the belief in a legal conspiracy has led these physicians to act in such a way as to perpetuate and even aggravate the very situation which they wish to eliminate. Their distrust of the legal system governing malpractice has engendered responses by this system which confirm this distrust. This self-fulfilling prophecy is most apparent with the suit-prone doctor. Such a doctor is more likely to provoke an emotionally based suit of questionable medical merit. His initial distrust of the legal system, reflecting his tendency to blame the system rather than himself, is reinforced by such a suit. Feeling threatened by the legal system, such a physician may attempt to retaliate by refusing to offer expert testimony. This tactic provokes new extensions of *res ipsa loquitur*, which further reinforce his distrust of the system.

The Double Bind

In a malpractice suit, however, the physician is confronted not only by his own internal conflicts but also by the public's conflicting attitudes toward the physician. Ordinarily, the public tends to re-

gard the physician as infallible and encourages him to behave as if he were; but in a malpractice suit, the physician is cast in a role diametrically opposed to his ordinary role. If he accepts the public's initial expectation of his infallibility, the challenge of a malpractice suit becomes unresolvable. In this way the public places the physician in a double bind from which the only escape is to retreat to a defensive position. Unable to admit to any error even to himself, the physician must either deny or justify his actions.

By restricting the definition of a physician's negligence to only those cases involving injury to a patient, the courts have further reinforced this defensive attitude. The physician has a hard enough time admitting to any error in public; but because of the additional guilt which he feels when his error leads to injury, he becomes even more defensive. It is also easy under the existing malpractice law for him to rationalize his defensive attitude by pointing to the high proportion of malpractice claims with little medical merit.

Toward a Peaceful Settlement

Legal Revisions

The legal profession has made it difficult for physicians to respond constructively to the challenge of malpractice. Even when physicians have tried to regulate medical practices, as in accredited hospitals, they have been frequently thwarted by the difficulty in obtaining legal sanction. A recalcitrant physician who has been denied hospital privileges may turn around and sue the hospital for depriving him of a means of livelihood; and it is often extremely difficult and invariably laborious to demonstrate in court sufficient grounds for the withholding of hospital privileges. Further support by the legal profession of physicians' efforts to regulate medical practices would help to encourage more of such efforts.

It has also been difficult for physicians to respond constructively to a malpractice law which simultaneously seeks to discipline negligent doctors and to compensate injured patients. By pursuing these divergent purposes under the aegis of one law, the courts have limited the legal sanction of malpractice to that small proportion of violations of the standard of care which leads to injury. Under such a law, the financial settlement is proportional to the seriousness of the injury; whereas the seriousness of the injury may bear little relationship to the quality of medical care. In part

due to this frequently haphazard relationship and to the withholding of the sanction from the many violations not resulting in injury, many physicians have developed a cynical attitude toward malpractice litigation as a means of maintaining a standard of care. The restriction of the sanction to those cases involving injury also selects cases in which physicians are least likely to admit to their error. Because of the guilt associated with injury to a patient, physicians in these instance are more likely to "justify" their behavior than to change it.

The present law also limits the right to recovery to a small proportion of the injured patients.

By subsuming under one law the enforcement of a standard of care and the right to compensation for medical injuries, the courts have severely limited the extent to which either objective can be achieved. Both objectives could be better achieved if the law were revised to make them independent of one another.

Abandoning an Illusion

The dual purpose of malpractice law, however, has been vital to enforcing a standard of care. Since the only legal sanction at present available to help enforce a standard of care is the payment of damages by the negligent doctor, the legal profession is not likely to relinquish this sanction without evidence that the medical profession will assume more responsibility for enforcing such a standard. Although the medical profession is not directly responsible for the present legal system governing malpractice, it can deny all responsibility for this system only at the peril of denying itself any constructive role in the future shaping of this system. While physicians have not formulated the present malpractice law, they have affected its formulation by their behavior—by failing to enforce a standard of care, they have obligated the legal profession to assume this responsibility; by refusing to give expert testimony, they have provoked the courts into extending the doctrine of *res ipsa loquitur*.

Physicians are deluding themselves if they expect that their repudiation of the legal system will make the system relinquish its authority over them. To the contrary, it can be expected that the legal profession will become more authoritarian in proportion to the degree to which the medical profession repudiates its authority.

Physicians also cannot expect the legal profession to initiate the changes they desire; for the legal profession does not share physicians' disaffec-

tion with the existing legal system governing malpractice. Lawyers personally have little to lose under this system; and plaintiff lawyers, with the lucrative fees available, may indeed have much to gain. In the main it is physicians, not lawyers, who are disturbed by the present system.

Yet by taking the attitude that they are being persecuted by the legal system and that the only way to contend with such a system is by opposition, physicians have selected the strategy which is least likely to bring about the changes they seek. Physicians can continue to repudiate the legal system and bear the consequences. But if they are to entertain any realistic hope of improving the situation, they will have to accept the present legal system as a *modus vivendi* while directing their efforts toward more satisfactory alternatives.

Coexistence

Adoption of this approach would imply several paths of action. It would imply cooperation with the existing legal system. Such cooperation would include a willingness to provide expert medical testimony in all malpractice cases. The establishment of medical expert panels represents a move in this direction.

It would also imply support of the recent efforts of many local medical societies in forming medical review boards to assist the malpractice insurance companies. These boards have reviewed malpractice claims and have rendered opinions on their medical merits, recommending contesting of unwarranted claims and settlement of legitimate claims. Defense lawyers and, increasingly, plaintiff lawyers also have come to respect these opinions, thereby avoiding much unnecessary litigation. The salutary effect of these boards gives some hint of the possible prospects of responsible cooperation with the legal system.

Self-Government

But beyond responsible cooperation with the existing legal system, successful efforts toward improving the regulation of medical practice will have to include more efforts by the medical profession to regulate itself. Physicians' most common criticism of malpractice law has been that lawyers and laymen are not properly equipped to evaluate the niceties of medical practice. Yet these same doctors have withheld testimony needed to reach an informed evaluation; while at the same time they have made little effort on their own to enforce a standard of care. Under these circum-

stances the legal profession has had little alternative to assuming responsibility for evaluating medical practices.

Professional Priorities

By conjuring a legal conspiracy, physicians have been able to legitimize their anxiety over the threat of malpractice. This maneuver has enabled them to suppress the more personal threat posed by a malpractice suit. But this gain has been purchased at the price of mounting anxiety at having to continually maintain a defensive position against an ever more powerful foe. This defensive position indeed has perpetuated the very problems of malpractice which it sought to eliminate, both in an objective sense by aggravating existing legal difficulties and prompting defensive medical care and in a subjective sense by conceptualizing the situation as a menace to be avoided rather than as a responsibility to be confronted.

Advice to physicians about malpractice has often supported this position by emphasizing ways to avoid malpractice suits.^{15,16} By implicitly recommending the practice of good medicine as secondary to avoiding a malpractice suit, such advice, albeit inadvertently, acknowledges and thereby revives the defensive mentality from which the specter arose. This preoccupation with the specter of malpractice has at times diverted physicians from their primary responsibility to provide good medical care. Were physicians to consistently regard good medical care as their primary responsibility, the specter would dissipate.

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The Role of Medicine in Aviation Safety

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THE CALIFORNIA MEDICAL ASSOCIATION'S symposium on the Role of Medicine in Aviation Safety, held in San Francisco, February 1 and 2, 1969, was the first in the nation devoted to this subject.

The interest in this subject was timely, for California is the largest center of aviation both as to operational flying, and to industrial research and development in aviation. The 85 participants were physicians, physician and dentist pilots, aviation medical examiners, commercial and general aviation pilots, airline stewardesses, airport personnel, nurses, governmental officials and members of the armed forces. The subjects presented were basic. They ranged from pilot physiologic aging through airport disaster planning. From free discussion in the course of formal presentations the following conclusions were drawn:

1. All pilots should give themselves a personal check-list of health status before they operate aircraft.
2. All large carrier hub airports having an employee census of 15 to 20,000 employees and a passenger census of 20,000 or more, should maintain a 24-hour emergency medical care facility. Minimum staffing should be by registered nurses, with emergency medical assistants of corpsmen status. A physician call-list with 15- to 20-minute availability must be required.
3. Airport disaster plans must provide for:
 - a. Crash site casualty care by mobile medical teams, not "first aiders" alone.

- b. A casualty reception center, manned by additional mobile medical teams, for further care of casualties after they have been removed from the crash site and before they have been taken to community hospitals for definitive care.
4. Federal Aviation Administration regulations for:
 - a. Standardization of emergency medical care training of flight stewardesses, with provision for recertification every two years.
 - b. Standardization of passenger life-support equipment aboard a carrier aircraft—in particular, oxygen equipment and emergency medical chests, (one for every 50 passengers).
 - c. Requirement that there be either a registered nurse, or an emergency medical assistant of corpsman type on all flights of five hours or more for present jet carriers or three hours or more for jumbo jets of 400-plus passenger capacity.
5. All hospitals that may function as casualty reception facilities should be urged to provide markers for helicopter landing or, when possible, roof-top heliports.
6. Studies should be continued on the effects of circadian rhythm disturbance on pilots and aircraft personnel, and work schedules should be arranged to provide maximum efficiency and lessen fatigue.
7. Study and further research should be carried out as to retirement of senior carrier pilots on a physiologic basis and demonstrated

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ability, rather than on chronological age of 60 years.

8. Multi-runway airports should be developed to permit handling of more planes at "peak" periods.
9. Decentralization of airport facilities should be carried out to handle increasing intercontinental flights.

A follow-up survey of the response of persons attending the symposium attested their active interest in this field. There was a strong request for annual meetings on the subject. There is at present no interdisciplinary council on aviation safety

either for California as a whole or regionally for either Northern or Southern California, and persons who attended the symposium expressed keen interest in the formation of such a council. The California Medical Association has been a pioneer in many fields of health services. Present day aviation is a vital factor in the lives of many Californians. Physicians must play a greater role in aviation safety. The California Medical Association should lead the way toward the establishment of a state council on aviation safety. The component societies of the CMA should be urged to participate in the formation of area councils. We have much to contribute in this field.

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EDITORIAL

Welcome NMA

WE EXTEND A WARM WELCOME to the National Medical Association which will hold its 74th Annual Convention August 10 to 14 in San Francisco. Elsewhere in this issue Julius W. Hill, the California physician who will be installed as the next president of the NMA, has given a most valuable account of the need for this organization, its growth, and particularly the important work that its component branches are doing in California. He notes that "almost one hundred percent" of the members of the Golden State Medical Association are also members of the California Medical Association.

One senses that the time is approaching when Negro physicians and Negro patients will become completely assimilated into the mainstream of medicine and then there will no longer be a need for a separate National Medical Association. This will be a truly great and important moment in the history of American medicine. We hope that it will come sooner and not later. In the meantime we wish the NMA well, and especially congratulate Dr. Hill and wish him a successful and productive term of office.

Portal Hypertension

ELSEWHERE IN THIS issue of CALIFORNIA MEDICINE is a review of the current status of portal hypertension by Richard P. Anderson and Earl F. Wolfman, Jr. There are probably few current

medical subjects that evoke greater controversy. Partly responsible for this are the patient, and institutional and geographical differences that exist with this disease. Whereas alcoholism is associated with the majority of cases of cirrhosis in this country, this is not the case in Great Britain, Africa and the Asiatic countries. Whereas cirrhosis is responsible for the great majority of cases of portal hypertension in this country and Europe, schistosomiasis and hepatoportal sclerosis (idiopathic portal hypertension) are more common in certain Asiatic and Arabic lands. And the disease in the indigent charity hospital patient generally behaves in a different fashion than in the well-to-do private patient. It thus becomes more understandable why successful treatment given to a patient in one area may not succeed in another setting.

While in agreement with the general outline and with the majority of the views expressed by the authors, I disagree with some of them. It will be recognized that this disagreement represents only a personal opinion and reflects the divergence of opinion which is literally world wide.

A classification of portal hypertension satisfactory to all has not yet been devised, and that outlined by the authors has its deficiencies. It is suggested that obstruction to portal venous inflow is congenital (cavernous transformation, atresia and stenosis) or due to thrombosis secondary to pylephlebitis following neonatal omphalitis or intra-abdominal infection. In fact, the causes are not known. Further, the evidence that pylephlebitis plays an etiologic role is so tenuous that it should be discarded. It is attractive and logical to think that an hepatic artery portal vein arterio-

venous fistula should be classified as extrahepatic and that it induces portal hypertension by the simple process of pouring a huge load of blood under arterial pressure into an originally low-pressure venous system. It is probably more complicated than that. Stone and co-workers in a major review of this problem presented evidence that such a fistula must exist for four years or more before clinical portal hypertension would develop. Our group has noted that the liver in such cases is not normal but exhibits subtle histologic changes which consist of increased portal fibrosis and eccentric sclerosis of the portal venules. This is the same histologic picture that is seen in idiopathic portal hypertension (hepatoportal sclerosis) and suggests that this hepatic lesion must develop before an arteriovenous fistula will produce clinical portal hypertension.

We think the term *cirrhosis associated with alcoholism* is slightly more appropriate than *alcoholic cirrhosis*, since the exact role of alcohol is still unknown. There must be some inherent susceptibility to the influence of alcohol in some persons, since cirrhosis develops in only about ten percent of chronic alcoholics in this country. Cirrhosis in the non-alcoholic has usually been called *postnecrotic* or *posthepatic*. Both imply viral hepatitis as being etiologic. This has not yet been proved and, until it is, more preferable terms would be *cryptogenic* or *idiopathic* cirrhosis.

In tube tamponade management of acutely bleeding varices, preference is given to the Linton balloon tube which, when properly inflated and fixed under tension to a well fitting face mask, will curb bleeding in almost all patients. It should be removed in 24 to 36 hours. Prolonged use may cause esophageal erosion near the cardia. This is especially true of the Sengstaken-Blakemore tube, the gastric balloon of which always distends in an eccentric fashion when inflated. When withdrawn and placed under tension, the inner firm rubber suction tube is displaced against the cardia. The firmness of this rubber tube can induce erosion quickly. The use of a pulley traction device has proved very unsatisfactory in our hands; failure to curb bleeding has occurred in almost 50 percent of patients. This is probably due to failure to maintain adequate tension because of friction of the rope over the pulleys. Further, it prevents the patient from moving his head from side to side. Most patients find themselves scooting down in bed in an effort to escape whatever tension is being exerted by the weights and pulleys.

Our thinking during the last two years concerning emergency or urgent operation for acute bleeding has been dominated by the influence of the syndrome of acute hyaline necrosis on immediate and late mortality. This disease only recently has been recognized as a clinical entity; synonyms are *florid cirrhosis*, *acute alcoholic hepatitis* and *steatonecrosis*. In a review of our emergency portacaval shunts we discovered that the operative mortality for those cirrhotic patients with superimposed acute hyaline necrosis was 84 percent. In contrast, mortality among those without this added lesion was 20 percent. Further, none of the usual features used to separate the good from the poor risk patients that have been employed by all workers in this field were of any value in identifying those with hyaline necrosis. Liver tenderness is a good identifying feature but this was present in only about half of our patients. Histologic examination of hepatic tissue is the only sure means of identification. Thus we now perform needle liver biopsy immediately on all patients admitted with acute bleeding. If hyaline necrosis is absent, emergency shunt is proceeded with; if present, nonoperative management is continued. This regimen has decidedly reduced the number of emergency shunts we now perform since so many of the alcoholic patients have hyaline necrosis. If the patient with acute hyaline necrosis survives the bleeding with non-operative management, a repeat liver biopsy is done about three months later if he has abstained from alcohol. This is about the length of time for this acute process to resolve. If resolution has occurred, he is offered an elective shunt.

Finally, I cannot concur with the authors' recommendation that a prophylactic shunt be recommended for all good risk and some fair risk patients who have varices but who have never bled. The studies of the Boston Interhospital Liver Group, the Veterans Administration Hospitals and of Conn and Lindemuth have quite conclusively established the ineffectiveness of shunting operations in prolonging life in these patients. Encephalopathy and liver failure are substituted for bleeding. Until more precise methods are developed to identify those patients who will do poorly after operation, prophylactic shunt should not be recommended.

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Abdominal Aortic Aneurysm: A Surgical Disease

ON PAGE 1 OF THIS ISSUE, Stoney and Wylie report their experience with 44 patients operated upon for ruptured abdominal aortic aneurysm. Their operative mortality of slightly more than 50 percent is comparable to that reported by most vascular surgical centers and points up the severe nature of this disease entity.

While improvements in operative and post-operative management may be expected to increase survival somewhat, the most important factor in improving survival is earlier operation. Mortality is significantly lower when operation is performed within one to two hours after the onset of symptoms, thus minimizing the shock period with its irreversible ischemic effects on the heart and kidneys.

In at least one-third of patients with rupture of aortic aneurysms, the condition is not diagnosed at the outset, and they are treated for hours or occasionally weeks with a mistaken diagnosis. Some patients are even operated upon with pre-operative diagnoses such as acute cholecystitis or other intra-abdominal inflammatory processes. Such operations by surgeons not trained in resection of a ruptured aneurysm greatly delay the definitive procedure and result in high subsequent mortality.

Fortunately few patients with abdominal aortic aneurysms succumb in the first few hours after rupture. The posterior peritoneum or vertebral column contains the leak for an average of several days and sometimes as long as weeks. This feature of the natural history of the disease should in most instances provide the opportunity for a correct diagnosis, particularly if ruptured abdominal aneurysm is entertained in the differential diagnosis.

Important features of the operation are preparing and draping of the abdomen with multiple intravenous catheters in place, if possible, before anesthesia is begun. Induction of anesthesia should be gentle to prevent full-blown rupture of the posterior peritoneum before the abdomen is opened. This is particularly important because many patients have died from straining during induction of anesthesia—all too often while the surgical team is still scrubbing. The first maneuver, once the abdomen is entered, is to gain

control of the aorta above its visceral branches away from the retroperitoneal hemorrhage. If severe hypotension is encountered at the beginning of the operation, manual compression of the accessible suprarenal aorta is carried out until the blood pressure is restored before any further operative maneuvers are performed. Prolonged hypotension during dissection of either the supra or infrarenal aorta may result in irreversible ischemia to the heart or kidneys, which will doom an otherwise successful operation to failure. High clamping of the abdominal aorta is tolerated for 20 to 30 minutes without irreversible ischemia to vital organs, and in that time infrarenal clamping can be secured. No attempt should be made to excise the posterior aneurysmal wall, thus simplifying and expediting the surgical procedure.

Once the aneurysm has been replaced with a graft, great care must be taken in releasing the aortic clamp lest proximal ischemia, particularly to the heart, be produced. Shunting of blood to the extremities can be tolerated only after systemic blood volume replacement has occurred. If the inferior mesenteric artery is patent and large or if the viability of the bowel, particularly the sigmoid, appears to be compromised at the end of the procedure, the inferior mesenteric artery should be reimplanted into the prosthetic graft, employing a small button of the aneurysmal wall with the origin of the inferior mesenteric artery. Patients with arteriosclerotic compromise of the celiac and superior mesenteric artery origins may also have aortic aneurysms. A patent inferior mesenteric artery may thus be vital to bowel viability. Such a precautionary measure as reimplantation of the inferior mesenteric artery may prevent a post-operative death in a patient of this type.

Blood replacement is monitored by the blood pressure cuff and central venous pressure. Frequent blood gas determinations postoperatively contribute significantly to the successful management of such patients. We have found that controlled ventilation with a volume-cycled respirator can be lifesaving in such patients, particularly the elderly in whom delay in diagnosis has resulted in prolonged shock. The oral intratracheal tube is allowed to remain in place for 72 hours if support is needed that long. Tracheostomy is carried out after this period if continued respiratory support appears to be necessary.

An experienced vascular surgeon thus employing the above technical procedures may be ex-

pected to salvage slightly better than one out of two patients with ruptured abdominal aneurysm who reach the operating room alive. Reduction in this continuing high mortality will be principally influenced by either earlier diagnosis and operation once rupture has occurred or by elective resection of the aneurysm before rupture. Operative mortality for an unruptured aneurysm averages 4 to 6 percent in skilled hands. It is of interest that the onset of symptoms in most patients heralds impending rupture and thus requires emergency surgical management. Operation at this time, before shock ensues, carries the low mortality associated with an elective procedure in an asymptomatic patient. Emergency operation in the symptomatic pre-rupture state is necessary because frank rupture can on occasion proceed with rapidity.

Every physician should be cognizant of the symptoms and signs of leakage in an abdominal aortic aneurysm. The cardinal symptom is sudden severe low back pain which is often accompanied by radiation to the back, flanks, pelvis, and groin. Signs of cerebral ischemia are also common at this time, depending upon the amount of blood lost into the retroperitoneal space. The confirming clinical sign is a palpable pulsating abdominal mass. While aneurysms 3 cm in diameter have been associated with rupture, the vast majority of those that rupture are 7 cm or more in diameter and are readily palpable.

Palpable aneurysm in a symptomatic patient warrants expeditious exploration. Such a patient may occasionally have both an unruptured aneurysm and other acute intra-abdominal disease, the latter causing the symptoms. A diagnostic error in such a patient will not cause his death; on the other hand, conservative management or even operation on a patient thought to have an inflammatory lesion but actually suffering from a ruptured aneurysm, may well delay the definitive treatment of a ruptured aneurysm if the surgeon is untrained in vascular procedures.

Elective excision and replacement of an aortic aneurysm can be safely performed in most patients regardless of the size of the aneurysm, the age and sex of the patient and the presence of associated disease. Patients with associated disease, moreover, can be expected to obtain a much longer life expectancy than that of patients not treated surgically. Surgical mortality is ten times less in patients with nonruptured than ruptured aneurysms. However, despite the continued high mor-

tality of patients with ruptured aneurysms, they must continue to be treated surgically, for survival without operation is exceedingly rare.

When more physicians appreciate the safety of the operation in experienced hands as opposed to the natural history of the disease, we can expect a decrease in numbers of patients seen with ruptured aneurysms. Furthermore, an awareness of the symptoms and signs of early rupture of abdominal aneurysms should permit earlier operation and, hence, significant improvement in mortality figures for operations performed even after rupture has begun.

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The Specter of Malpractice

IN THIS ISSUE a new category of articles, *Student Contributions*, makes its start with a communication titled "The Specter of Malpractice," by Geoffrey E. Linburn.* We are publishing the article for two reasons. One is that we believe mature physicians and thoughtful students both can benefit from communications of this kind. More important, we believe that the author makes some points which the profession should hear.

To physicians with knowledge of the many programs that the California Medical Association is carrying on to assure good medical care and to protect patients from damage that may be done when they do not get it, cursory reading of the article will disclose some poorly founded assumptions and statements by the author. The items in question are to some extent attributable to reliance on dated sources, probably because more recent information is generally less publicized. They do, however, serve to call attention to the considerable progress that medical organizations have made in this field. For instance, Dr. Linburn relies on articles or statements which appeared in 1956-57. Those familiar with malpractice litigation and professional activities are aware that there have been great changes in the last dozen years. The author also seems unaware of vigorous efforts at many levels in the medical profession in California to improve practice and to enforce proper standards

*The author was a fifth year student at the Stanford University School of Medicine at the time he submitted the article; is now a Doctor of Medicine intern at Denver General Hospital.

of care. It is to be hoped that our young physicians will participate in the activities of society professional relations committees, peer review committees, hospital staff credentials, utilization, tissue and related committees, in CMA hospital survey committees, and in numerous similar efforts. Any physician accepting such responsibilities will quickly realize that California's physicians spend a great deal of time seeking to enforce the requisites of good medicine. As the author of "The Specter of Malpractice" notes, these efforts are laborious and may be thwarted by legal maneuvers. However, there is abundant evidence to dispel any belief in a "frequent, tacit agreement among physicians, not to hold one another accountable for a standard of care."

These errors should not distract from the very valid points which the author makes, among them that blaming the courts or the legal profession will not solve medicine's problems.

Affirmative efforts are necessary, based upon comprehension of public attitudes. The success of these efforts requires knowledgeable participation by individual physicians, as well as their professional societies.

Power Tactics in Health Care

POWER PLAYS of one sort or another are becoming the order of the day in health care. For evidence that this is so one need only cite recent organized strikes by nurses, not only for wages, but for more administrative control of patient care as well; "heal-ins" conducted by associations of interns and residents for better working conditions and more pay; and, in another vein, certain clearly discriminatory uses of government power with respect to mandatory and arbitrary reductions of physician fees for services they have rendered. Practicing physicians have not been accustomed to such power

tactics in health care and they are ill equipped to engage in this sort of conflict. Yet it is clear that health care is becoming an arena for social, economic and political conflict in our society and power plays of one sort or another are becoming an accepted part of the health care scene.

When one is set upon, whether it is by nurses, labor unions, government or even a physical assailant, there can be only three possible responses—surrender, counteraction, or no action (which is the non-violent position where one is only speaking of violence). Surrender is obviously totally self-defeating. Counteraction may also result in defeat, or perhaps in the defeat of the attacker; or, if neither of these occurs, some sort of balance of power may develop which may be more or less enduring. No action—that is, neither surrender nor counteraction—is ennobling to the soul and can sometimes be successful, provided one is willing to risk one's all for it; but in reality no action leaves most of the immediate options in the hands of those who would use power tactics to impose their will.

Like it or not, the medical profession and medical organizations are perforce participants in this arena of conflict in health care and they should not only hold their own but be among the strongest of the participants. To this end it would seem that when the inevitable conflicts come about, a policy of counteraction would usually be preferable to accepting the penalties of surrender or of no action. This of course implies that the medical profession will master the techniques of such power tactics as may be needed, become competent in their use, and be willing to use them in whatever conflict situation may arise. This will be a clear departure from traditional professional attitudes, but so is the growing acceptance and use of power tactics in health care. We had best get on with it as quickly as possible. The alternatives are becoming increasingly unacceptable in the interests of better medicine and better health care.

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H. Director, State Department of Public Health

Laboratory Diagnostic Services For Rubella in Public Health Laboratories in California

THE STATE DEPARTMENT OF PUBLIC HEALTH has received a number of inquiries from physicians concerning laboratory tests for diagnosis of rubella. The department's Viral and Rickettsial Disease Laboratory has offered such tests since early in 1965. Intensive development and evaluation studies have resulted in significant improvements, both in virus isolation and serologic methods, which greatly broaden the practical applications of rubella laboratory tests in clinical practice. Thus, the State Virus Laboratory now offers tests:

- To confirm or rule out rubella in patients with exanthem or other suspicious clinical signs of rubella,
 - To establish the diagnosis of congenital rubella virus infection in infants,
 - To determine the immunity status of pregnant women exposed to rubella during pregnancy.
- Tests for immunity are also provided for nurses and other medical personnel subject to high risk of exposure.

Other important uses of rubella tests include routine testing of women for immunity status at time of prenatal examination or before they become pregnant. With the release of attenuated live rubella virus vaccines expected shortly, the need for immunity tests will increase since tests for presence of rubella antibodies in women of child-bearing age will offer a means of identifying those who are susceptible and may benefit from immunization. However, because of the overwhelming volume, the State Virus Laboratory cannot offer routine prenatal or pre-vaccination tests. Moreover, this need can be met most effectively through development of local laboratory resources.

The laboratory resources needed to carry out testing on so large a scale are not available in California. To provide such laboratory assistance to individual physicians and community health fa-

cilities will require that additional laboratories in various localities in California develop competence in performing tests for rubella.

To this end the State Health Department's Virus Laboratory has assisted a number of local public health department laboratories to acquire experience in rubella test methods. Several now offer this service locally and others are in the process of training personnel. A few clinical laboratories in California now offer serologic tests for rubella. Laboratories which have not had previous experience in the field of viral serology, however, face serious difficulties in undertaking tests for rubella until specialized professional training and experience with the tests have been acquired.

A clear warning of these difficulties was recently issued by the Medical Laboratory Services Advisory Committee of the U.S. Public Health Service as follows*:

"Serologic Testing for Rubella— A Warning"

"Serologic tests for rubella are primarily used to determine: (1) the immune status of individuals in a given population; (2) the immune status of pregnant women who have been exposed to rubella; and (3) the etiology of cases of exanthematous disease. In the first instance, results of tests are used for epidemiological and immunization planning purposes; in the second and third instances, results are used to provide information for making medical management decisions in situations of some urgency.

"At the present time the hemagglutination inhibition (HI) test is the technique most widely used for measuring rubella antibodies. This test is a complex procedure which must be performed by well trained, experienced individuals. In addition, a thorough knowledge of the immune response is essential for the proper interpretation of test results. Because of actions which may be taken on the basis of laboratory results, the need for accuracy is great, and certain problems associated with the HI test must be recognized.

"The HI test for rubella is not a standardized

Reprint requests to: Viral and Rickettsial Disease Laboratory, State Department of Public Health, 2151 Berkeley Way, Berkeley 94704.

*Quoted from the U.S. Public Health Service's weekly report "Morbidity and Mortality," Vol. 18, p. 126, 12 April 1969.

technique, and several modifications of the basic procedure are in use. Methods for removing non-specific inhibitors in serum specimens may not be completely effective, or they may remove specific antibody, leading to false positive or false negative results. Reagents obtained from different sources are not uniform in quality or in suitability for all modifications of the HI test. Since the products from each manufacturer are for use in a specific HI procedure, intermixing reagents from different sources can lead to problems in test performance. Further, the wide variability of erythrocyte suspensions has considerable bearing on the sensitivity of the test. Because of the lack of uniformity in testing procedures and reagents, interpreting laboratory results is a sophisticated undertaking, and, of necessity, may vary from one laboratory to another.

"In view of the problems associated with this serologic procedure, HI tests for rubella should not be attempted in a laboratory carrying out the tests on an infrequent basis. Such a laboratory cannot maintain the necessary skills and controls, and, in urgent cases involving therapeutic abortion, pressures may lead to failure to repeat tests or to perform more difficult supplemental tests, such as complement fixation, fluorescent antibody, and serum neutralization tests, or IgM determinations which may be necessary for accurate interpretation.

"The laboratory asked to carry out HI tests for rubella only infrequently or to perform supplemental tests for which it is not qualified should refer diagnostic materials to a state health department or other competent reference laboratory."

Standardizing Methods and Training Personnel

The Virus Laboratory of the California Department of Public Health is collaborating with the National Communicable Disease Center (NCDC) to assess various modifications of the HI antibody test procedure to assist in establishing recommendations for an optimal standard method. The NCDC and state laboratories also perform tests with commercially distributed rubella test "kits" and reagents to evaluate performance. Difficulties have occurred in performing the test with some of the commercial products.

The laboratory Proficiency Testing Program recently initiated by NCDC provides that each participating State laboratory test identical specimens and compare their results with those of selected

reference laboratories. The state laboratories can thus recognize deficiencies in the quality of their results and seek out sources of error.

In California, local public health laboratories that perform tests for rubella may send representative specimens, together with their own results, to the State Health Department Virus Laboratory for confirmation. If significant discrepancies occur, consultation and assistance are available to define and correct the error.

The State Virus Laboratory is conducting workshops on the rubella HI test to assist in training of local public health laboratory personnel. Instructions are given on the recommended procedure, sources of satisfactory reagents and problems in interpretation of results. To be eligible for these workshops, applicants must be graduate microbiologists with at least six months' experience in a public health laboratory, or equivalent. In addition, the virology program for microbiologist trainees at the State Virus Laboratory includes thorough instruction in rubella HI tests. Representatives from 25 local public health laboratories have completed this training. The experience gained by these laboratories will offer a local resource to help other local laboratories become proficient in the rubella HI test.

Clinical laboratories contemplating rubella HI tests should have an experienced microbiologist who has obtained specific training in this procedure.

Interpretation of Rubella Serologic Tests

In clinically apparent infections of children and adults rubella HI antibodies generally appear by three to five days after onset of symptoms and increase to a maximum titer by 14 to 21 days after onset. Antibodies persist thereafter for many years, perhaps for life, gradually declining in titer. There are pronounced individual variations in the maximum antibody reached and the duration of highly elevated titers. One patient at two weeks after onset may have the same antibody titer as another who had rubella two or three years ago. Thus, for serologic tests to be useful for supporting clinical judgements, especially those concerned with rubella, or exposure, in pregnancy, the time at which specimens are collected is of critical importance.

For confirmation of a suspected case of rubella, it is essential to demonstrate a significant rise in antibody titer between two serum specimens, the

first drawn promptly after the appearance of the rash or other clinical signs, and the second at 14 to 21 days. Only a few days' delay in obtaining the initial specimen may preclude judgement as to whether an antibody titer is related to the present illness or represents residual antibody from a past infection.

To determine if a patient is already immune at the time of exposure to a case of rubella, the serum must be obtained promptly, preferably within seven days, but no later than ten days, after the exposure. After ten days, it becomes increasingly uncertain whether any antibody demonstrated reflects existing immunity at the time of exposure or an infection subsequently acquired. When a single specimen obtained promptly after exposure shows the presence of antibody, the patient is considered to be immune and follow-up specimens are not usually needed.

When paired specimens are tested to demonstrate a change in antibody titer, they must be tested simultaneously, utilizing the same reagents and identical test conditions in order to minimize inherent variations in the test. Hence, the first specimen is held by the laboratory until the second is received and can be tested together with the first.

Specimens for Rubella Serologic Tests

In summary, the specimens for serologic tests should be collected as follows:

Type of specimen: 6 to 8 ml of whole clotted blood; no preservative.

1. For diagnosis of clinical case; submit two specimens.
 - a. Acute-phase as soon as possible after onset (after five days may be too late to show diagnostic rise in antibody titer).
 - b. Convalescent-phase, 14 to 21 days after onset.
2. For immunity status at time of exposure; submit one specimen as soon as possible after exposure; no later than seven to ten days.

Information to Accompany Specimens

For the laboratory to proceed intelligently and interpret test results a request form must accompany the specimen providing pertinent information on the clinical circumstances which have prompted the request as follows:

- Identification of patient: Name, age, sex.
- Date specimen collected.
- Reason for test; indicate clearly whether for:

- a. suspected clinical case
 - b. exposure only; no clinical signs
 - c. suspected congenital infection
 - d. other circumstances; e.g., nurse, subject to exposure in clinic.
- If clinical case: give date of onset.
 - If exposed only: give date(s) of exposure.
 - Indicate if patient is pregnant: give date of last menstrual period or estimated week of gestation.
 - If suspected congenital infection: give date of birth, signs of congenital rubella, maternal history of rubella.

Public Health Laboratories Performing Tests

As services are now available locally or soon will be in various areas, local laboratories or physicians wishing to obtain tests for rubella are advised to contact their local health department for information.

In those jurisdictions where services are not available, the Virus Laboratory of the State Health Department will perform tests for rubella upon submission of appropriate specimens and clinical information as outlined above. *The State Virus Laboratory, however, is unable to provide routine prenatal immunity testing, routine testing in anticipation of pregnancy, or administration of vaccine.*

Laboratories of the local health departments listed below are now or soon will be offering tests for rubella. In these areas, to avoid delays, requests for rubella tests should be submitted directly to the local laboratory and the local laboratory should be contacted regarding request forms, specimen containers, or instructions for submitting specimens:

Alameda Co. Health Dept.,
Oakland, 499 5th St.
Contra Costa Co. Health Dept.,
Martinez, 1111 Ward St. (P.O. Box 871)
Fresno Co. Health Dept.,
Fresno, 515 So. Cedar Ave.
Los Angeles Co. Health Dept.,
Los Angeles, 220 N. Broadway
Orange Co. Health Dept.,
Santa Ana, 645 No. Ross St. (P.O. Box 355)
San Diego Co. Health Dept.,
San Diego, 1600 Pacific Highway
Santa Clara Co. Health Dept.,
San Jose, 2220 Moorpark Ave.
Yolo Co. Health Dept.,
Woodland, 10 Cottonwood St.
(P.O. Box 1157)

LETTERS *to the Editor*

School Health-History Forms

To the Editor: I read Dr. Smilkstein's article in the April 1969 issue of CALIFORNIA MEDICINE—"School Health-History Forms"—with considerable interest as I have been encouraging revision of those used in our school system. Our high school nurses, in many instances, feel our health inventories are a waste of their time.

Since we don't do routine examinations in our schools and do not get requested health examination reports for many of our students entering junior and senior high schools, I am in agreement with the author regarding the value of a good health inventory. However, I am afraid the use of a form such as Dr. Smilkstein suggests would be entirely unsatisfactory in an urban school system such as ours where the reading level of a large population is below average and high school biology is an elective subject. The assistance of a school nurse or science teacher would be required to answer many of the questions. Without this assistance the answers would be completely unreliable.

If the school population where Dr. Smilkstein works is either average or above average scholastically, it would be interesting to try the suggested inventory and to determine how valid and worthwhile such a questionnaire would be. I would suggest, however, that if it is to be used in urban school districts that the language be drastically changed, particularly if help cannot be provided by a nurse or teacher to assist pupils in completing the questionnaire.

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And the Author Replies

I have been given the opportunity to read your [Dr. Leah L. Hirsch's] letter of June 12, 1969 in which you comment on the "School Health History Form."

I must suggest that you underestimate the capabilities of our secondary school students. I shared your concern regarding the language in the form. Prior to the completion of my paper the suggested health history form was given to teenagers in the Upward Bound Program sponsored by the Office of Economic Opportunity in Claremont. These youngsters are from socio-economically depressed areas (Blacks and Chicanos) and they completed the forms with little trouble. The School Health History Form gave us an excellent view of the health picture of this group.

It is not expected that the students should understand all terms (Osgood-Schlatters for example). It is expected that those students who have had exposure to a given illness or injury would recognize and mark the item on the form.

In our concern for a satisfactory inventory we must not lose sight of the fact that our present health evaluation in California leaves much to be desired. I would vote for a conference to develop an ideal statewide form.

G. SMILKSTEIN, M.D.
Claremont

Treatment of Shock Following Myocardial Infarction

JAY N. COHN, M.D.

Material supplied by the California Heart Association

WHILE NEWER REFINEMENTS in patient monitoring and management have significantly reduced the mortality from acute myocardial infarction, the occurrence of shock still carries a grave prognosis. Once shock develops the survival of the patient is entirely dependent on the perception, attentiveness and judgment of his physician.

Shock is characterized by a critical reduction in tissue perfusion. Inadequacy of blood flow impairs organ function and disrupts the integrity of normal metabolic pathways. If shock is not promptly corrected, the flow deficiency leads to organ damage, metabolic acidosis and a vicious circle resulting in progressive circulatory deterioration and death. The sooner the syndrome can be recognized the more likely is therapy to be effective. The need for prompt recognition of shock must not, however, be satisfied at the expense of "over-diagnosis." It is in this initial evaluation that the physician's perceptiveness is critical. He must be able to recognize the difference between the mildly hypotensive patient who is adequately perfusing his tissues (and needs no immediate treatment) and the patient who is in the incipient stages of shock and requires prompt therapy to restore peripheral blood flow.

In considering the diagnosis of shock, attention should be given to the following signs:

Skin temperature. Warm skin indicates adequate cutaneous blood flow and usually a fairly well maintained cardiac output. Cool, clammy skin indicates sympathoadrenal discharge, a sign of reflex vasoconstriction in response to a fall in cardiac output.

Peripheral pulses. Thready or absent brachial and radial pulses indicate either severe hypotension or more often intense vasoconstriction. In either case urgent treatment is indicated. Femoral artery pulsation will be very weak if the patient is hypotensive but the pulsations are bounding in the presence of peripheral vasoconstriction.

Auscultatory blood pressure. This is not a reliable guide to intra-arterial pressure in shock. A low cuff pressure has the same significance as weak upper extremity pulses. However, an absent auscultatory pressure usually indicates inadequate blood flow and the need for treatment.

Mentation. If the patient is alert and responsive cerebral blood flow is probably adequate. Agitation, confusion or somnolence are signs of deficient cerebral blood flow and usually are associated with a fall in arterial pressure.

Urine output. Urine flow less than 20 ml per hour with a low urine sodium concentration is evidence of inadequate renal blood flow which if not corrected can lead to tubular necrosis.

Cardiac function. Persistent or recurrent chest pain or arrhythmias in the presence of other signs of hypotension may be accepted as presumptive evidence of functional impairment of coronary blood flow.

Acidosis. Low arterial blood pH and elevated blood lactate mean reduced tissue oxygenation. Arterial blood gas and pH studies are invaluable in the management of patients in shock.

The presence of one or more of the above signs of inadequate tissue blood flow in a patient with an acute myocardial infarction is presumptive evidence of shock. Mild hypotension in the absence of any of these signs should not be diagnosed or treated as "shock."

When the diagnosis of shock has been made, several questions regarding the hemodynamic status of the patient should be answered before definitive treatment can be instituted:

Is the patient severely hypotensive? Hypotension is an immediate threat to life because of the associated impairment in cerebral and coronary blood flow. Since the cuff pressure may be low even though arterial pressure is normal, the strength of femoral arterial pulsation often is a more reliable guide to blood pressure. In some patients direct recording of arterial pressure may be necessary.

Is blood volume adequate? Some patients become

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hypovolemic in the hours following an acute myocardial infarction and the reduction in plasma volume may then become an important factor in the genesis of shock. The central venous pressure (CVP) is a vital guide to the adequacy of circulating volume and should be monitored in all patients with shock. This can be accomplished by threading a catheter through a needle in the brachial, femoral or subclavian vein and advancing it into the thorax. A low CVP (less than 6 cm of water with the zero level at the mid-chest) is an indication for a trial of volume expansion. In myocardial infarction the left ventricle often is in failure while CVP is normal. Therefore, volume expansion should be carried out cautiously. A rise in CVP of more than 2 cm of water during infusion of dextran, saline or other fluid indicates that volume has been adequately restored. If shock is not corrected by volume expansion the presence of significant left ventricular failure can be assumed.

Is cardiac function severely impaired? If peripheral blood flow is decidedly reduced and the CVP is high, then myocardial failure is obviously an important factor in the shock. Heart rate is not a very useful index of cardiac function. Indicator dilution cardiac output data are of value in the evaluation of myocardial function in selected cases.

What is the status of the peripheral vessels? Is there evidence of intense sympathetic discharge? This usually is manifested by cutaneous vasoconstriction and indicates renal vasoconstriction as well. In early stages of shock peripheral constriction may support fairly normal arterial pressure despite progressive tissue hypoperfusion and lactic acidosis.

The purpose of therapy in shock is to restore adequate organ perfusion. Effective therapy must be based not only on an understanding of the physiological disturbance in the individual patient but also on a thorough understanding of the pharmacological action of the useful drugs.

The following drugs may be valuable in certain patients with cardiogenic shock:

Isoproterenol. This is a catecholamine with pure beta adrenergic activity; that is, it stimulates the heart and dilates peripheral vessels. It is probably the agent of choice when impairment of cardiac function has led to severe reduction in cardiac output, especially when reflex vasocon-

striction is present. Isoproterenol 1 or 2 mg should be diluted in 500 ml 5 percent dextrose in water and the rate of infusion gradually increased until the signs of shock are corrected or cardiac rhythm disturbance limits further administration. In some cases the concentration of isoproterenol must be increased as much as 2 mg per 100 ml to obtain a satisfactory effect. Lidocaine may be effective in controlling ventricular irritability during isoproterenol infusion. In some hypotensive patients isoproterenol will not significantly increase arterial pressure and cerebral and coronary perfusion are not improved. In this situation a vasoconstrictor-inotropic agent may be necessary.

Levarterenol (Norepinephrine) or metaraminol. These drugs have an alpha adrenergic effect (vasoconstrictor) on peripheral vessels combined with myocardial stimulating properties. Because these drugs may reduce renal and splanchnic blood flow they should be used only when isoproterenol is ineffective. The infusion rate should be the smallest amount necessary to increase systolic arterial pressure over 100 mm of mercury.

Digitalis. The cardiac glycosides have inotropic effects less potent than the catecholamines. They also have vasoconstrictive properties when used intravenously. It is probably best to treat cardiogenic shock acutely with the adrenergic inotropic drugs above and to administer digitalis orally for its more sustained effect.

Atropine. If shock is associated with sinus bradycardia, 1 mg atropine intravenously may be effective in restoring heart rate and blood flow. Drugs, such as atropine and isoproterenol, which result in an increase in atrial rate must be used cautiously in the presence of atrioventricular block. In these circumstances, an increase in atrial rate may result in a decrease in ventricular rate.

Furosemide. This potent diuretic can help establish urine output in the oliguric patient. After shock has been treated with the vasoactive compounds above a diuretic response to intravenous infusion of 200 mg of furosemide indicates that renal perfusion is adequate. If oliguria persists, however, more aggressive attempts to improve blood flow are necessary.

Sodium Bicarbonate. If the arterial pH is less than 7.35, sodium bicarbonate should be administered in amounts adequate to restore pH to

above that level. Treatment should be initiated with 40-100 meq sodium bicarbonate and further alkali therapy based on arterial blood pH measurements.

Ventricular pacing. If shock and marked bradycardia co-exist, increase in ventricular rate via catheter electrode pacing is often of great clinical benefit.

Newer pharmacological approaches such as the use of sympathetic blocking agents and other inotropic drugs, such as dopamine and glucagon, are still in the experimental stage.

Effective management of shock requires not only initiation of the correct therapy in the correct amounts, but also close continuous monitoring of cardiovascular function. Adrenergic drugs should be weaned and discontinued as soon as possible. Blood volume may be inadequate after cardiac function is improved, and a falling CVP may be an indication for administration of dextran, even in patients who have manifested heart failure only a few hours before. If rhythm disturbances persist electrical pacing through a transvenous pacemaker may help improve peripheral blood flow.

It is clear that intelligent use of the means currently available can be effective in salvaging many patients who would otherwise succumb to cardiogenic shock. In others, however, the impairment in cardiac performance is so severe that medical therapy is ineffective. In this selected group of patients mechanical means of temporary circulatory support may eventually become an important adjunct to management.

Pesticide Poisoning May Appear Anywhere

A Statement prepared by the Committee on Occupational Health of the California Medical Association in cooperation with the Bureau of Occupational Health, California Department of Public Health.

CONTAMINATION OF CONSUMER goods from spills of toxic chemicals occurring in storage and transit have resulted in bizarre and tragic episodes of poisoning involving hundreds of people. Incidents of less severe nature, but somewhat similar to those that have occurred in Colombia, Saudi Arabia and Mexico, have taken place in California. The in-

creasing amount of such materials being transported and stored in California increases the probability of further accidents here. Significant contamination can occur from a very small amount of a very toxic pesticide and a poisoning may result from either ingestion or skin absorption. There has been an increase in spills of toxic pesticides due to containers falling from trucks on the highways. There has also been an increase in the use of such pesticides for suicidal purposes.

Every physician in California, whether practicing in an urban or a rural area, should be able to recognize and treat promptly poisoning from phosphate ester pesticides. This capability can frequently save lives of poison victims who have absorbed several potentially fatal doses.

The antidotes for poisoning by these anticholinesterase chemicals are large doses of atropine and Protopam chloride.* An adequate supply should be readily available to the physicians and hospitals in all areas of the state.

There are hundreds of pesticides ranging in wide degrees of toxicity. The name or type of chemical must be known before specific treatment can be instituted. However, it is the phosphate ester pesticides with which the physician should be most familiar. Among the most toxic are TEPP (tetraethylpyrophosphate), Phosdrin® (alpha isomer of 2-carbomethoxy-1-methylvinyl dimethyl phosphate), parathion, methyl parathion, Thimet® (phorate), Di-Syston® (sulfur analog of demeton), and Systox® (demeton).

Diagnosis and Treatment

Signs and symptoms are explainable on the basis of cholinesterase inhibition. Symptoms may be delayed for several hours after last exposure, but rarely for a longer period than 12 hours. Early or mild poisoning is hard to identify since it can be confused with other conditions, such as heat exhaustion, gastritis, encephalitis, asthma, pneumonia, or other respiratory infections. Glycosuria can be found in 30 percent of the cases and diabetic coma mistakenly considered. Symptoms most often appear in the following order: headache, fatigue, giddiness, nausea, salivation, sweating, blurred vision, tightness in chest, abdominal cramps, vomiting, and diarrhea. In severe poisoning, difficult breathing, tremors, convulsions, collapse, coma, pulmonary edema, and respiratory

*Protopam chloride® (pralidoxime chloride, 2-PAM) is a product of the Ayerst Laboratories, Inc., New York, N.Y.

failure follow. Pupils are constricted in about 80 percent of the cases, but in the remainder may be dilated.

The more advanced the poisoning the more obvious are the typical signs: myosis, rapid asthmatic breathing, and pronounced weakness coupled with excessive sweat and accumulation of bronchial fluids. If the picture is clear, treatment should begin at once even if a history of exposure is not obtained.

A red cell and plasma cholinesterase test should be performed when phosphate ester poisoning is suspected. In adults with symptoms, the red cell cholinesterase activity is usually reduced to below 0.20 Δ pH per hour and may approach zero in severe poisoning. The red cell test reflects the initial clinical state of the patient at the time of the testing. Victims of fatal poisoning should have blood and brain cholinesterase determinations to avoid a missed diagnosis.

Treatment

1. Support respiration. This is of great importance since death is usually from respiratory failure.
2. Decontamination. Remove contaminated clothing; wash skin, hair, and fingernails with soap and water; if in eyes, irrigate for 15 minutes with normal saline solution or water; if ingested, induce vomiting or wash stomach and give saline cathartic.
3. Atropine sulphate in large doses after cyanosis is overcome (atropine given to a cyanotic patient may induce ventricular fibrillation). Inject 2 to 4 mg intravenously every 5 to 10

minutes until signs of atropinization appear. Twenty-five to 30 mg may be necessary during the first day.

4. Give Protopam chloride. For severe adult poisoning, inject 1 gram intravenously slowly; give second dose of 0.5 gram in about 30 minutes if muscle weakness is not relieved or recurs. Children's doses should be proportioned by body weight.
5. Watch patient continuously. Emergency lasts 24 to 48 hours.
6. Cholinesterase test*: 10 ml of blood, use heparin as anticoagulant, preferably before giving Protopam chloride. Start treatment without waiting for results.
7. Contraindicated: morphine, aminophylline, theophylline, reserpine, phenothiazin tranquilizers, and large amounts of fluids intravenously. Barbiturates should be used only with great care.

Workers should not take atropine or Protopam chloride as a prophylactic measure nor should they be issued such material for first aid purposes. Poisoned workers should not return to jobs handling phosphate esters until their plasma and red cell cholinesterase has returned to normal. This may take several weeks in the case of the former and as long as a month in the case of the latter.

*Cholinesterase is an enzyme found in many body tissues. It is a simple clinical laboratory procedure to measure cholinesterase activity of plasma and of the red blood cell. The enzyme is inhibited by organic phosphate-type pesticides and, as a result, plasma and red blood cell cholinesterase activity is decreased.

The Michel Electrometric Method is the most widely-used technique for measuring cholinesterase activity. The results are reported in Δ pH units per hour. The normal range for the method is wide, with an average of about 0.77 Δ pH units per hour for red cells (range, 0.39-1.02) and an average of 0.95 Δ pH units per hour for plasma (range, 0.44-1.63). The laboratory performing the cholinesterase test should provide information on the normal values for the method used.

DETECTING ALLERGIC SENSITIVITY IN A CHILD

"A very useful laboratory technique [for detecting an allergy in a child] is the nasal smear, which is quite simple and can be done in 60 seconds by your office technician. Nasal smears are not helpful, however, in the first three months of life because of a physiologic nasal eosinophilia. But after the age of three months, the presence of 10 percent or more eosinophils in the nasal smear is very strong evidence for the presence of allergy."

—GEORGE BRASHER, M.D., Temple, Tex.
Extracted from *Audio-Digest Pediatrics*, Vol. 14, No. 22, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Council Highlights

Highlights of the Actions of the California Medical Association Council Meeting, May 9 to 10, Sacramento

This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA office.

553rd Meeting, May 9 to 10, 1969, Sacramento

A draft of the 1969 CMA *Relative Value Studies* was approved. The effective dates for general distribution and use of the *RVS* will be determined later. Copies of the approved draft have been distributed to executive secretaries of county medical societies in California and other state medical associations.

A proposal to study treatment of obesity by unscientific methods was approved. The recommendation calls for CMA and the State Department of Public Health to study "the extent and degree of danger" of unscientific methods for treatment of obesity. CMA's House of Delegates this year and in 1968 passed resolutions urging CMA and AMA to take action on treatment of obesity.

Future steps to be taken after completion of the study, which CMA Council approved with the study proposal, will be as follows:

- County medical societies investigate physicians who use unscientific methods to treat obesity; talk with the offenders and take disciplinary action if they do not change.
- CMA work with voluntary and official health agencies to alert people to the dangers of drugs in treatment of obesity.

- CMA make a recommendation to the Board of Medical Examiners for action and investigation of non-members of county medical societies who are using unscientific methods of treatment of obesity.

Formation of a CMA Standing Committee on human organ transplantations was approved. In addition to its other responsibilities, the new committee will respond to a request from Louis F. Saylor, M.D., director, State Department of Public Health, for CMA representatives to discuss with his department "problems which are emerging from accelerated activities in transplantations of human organs."

ALBERT G. MILLER, M.D. President
 RALPH W. BURNETT, M.D., Bakersfield . . . President-Elect
 WILLIAM F. QUINN, M.D. Speaker
 JOSEPH F. BOYLE, M.D. Vice-Speaker
 RICHARD S. WILBUR, M.D. . . . Chairman of the Council
 HAROLD KAY, M.D. Vice-Chairman of the Council
 HELEN B. WEYRAUCH, M.D. Secretary
 MALCOLM S. M. WATTS, M.D. Editor
 ROBERT L. THOMAS Executive Director
 General Office, 693 Sutter St., San Francisco 94102 • 415 776-9400
 PAUL S. PARRY Southern California Office
 3345 Wilshire Blvd., Suite 500, Los Angeles 90005 • 213 380-8272
 RICHARD W. LEMOS Sacramento Office
 1127 11th St., Sacramento 95814 • 916 444-5532

The Role of Medicine in Society Committee was authorized to contact the appropriate student body of each medical school and request names of students to invite for participation in: (1) Council meetings; (2) CMA House of Delegates meetings; (3) specific commission and committee meetings, and (4) specific areas of involvement such as drug abuse, smoking and medical education.

Appointment of Orrin S. Cook, M.D., Sacramento, as a consultant to the CMA Legislative Committee was approved.

Appointed to the new Task Force on Allied Health Professions were: Gladden V. Elliott, M.D., San Diego, chairman; L. H. Andrus, M.D., King City; Lewis Bullock, M.D., Los Angeles; Arthur Coleman, M.D., San Francisco; Earle Marsh, M.D., San Francisco; Frank Melone, M.D., Ontario, and E. Kash Rose, M.D., Napa.

A program committee and early plans for the 1969 Conference of Component Society Officers on

27 September in Los Angeles was approved. Topics will include professional liability; medical student involvement; new methods of delivering health care; recertification through continuing medical education and professional corporations. Program Committee members are: Roberta Fenlon, M.D., chairman; Frederick W. Ackerman, M.D.; Leonard M. Asher, M.D.; Ralph M. Milliken, M.D.; Robert L. Hippen, M.D.; Herbert A. Holden, M.D.; Austin W. Lea, M.D.; and William K. Scheuber.

A State Senate resolution commending CMA President-Elect Ralph W. Burnett, M.D., on his outstanding career in medicine was presented to him by State Senator Walter W. Stiern (Dem.-Bakersfield).

The CMA Commission on Community Health Services was requested to study and bring back recommendations on CMA's role in fluoridation with particular attention to the extent and scope of a CMA program.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

ASHER, ROLAND SANFORD, Encino. Died 12 May 1969 of injuries in an automobile crash on the San Diego Freeway, aged 45. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1953. Licensed in California in 1954. Doctor Asher was a member of the Los Angeles County Medical Association.

✧

CHASE, JAMES MACKAY, Santa Barbara. Died 27 May 1969, aged 47. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1955. Licensed in California in 1956. Doctor Chase was a member of the Santa Barbara County Medical Society.

✧

COOPER, WILLIAM WARREN, San Diego. Died 14 May 1969, aged 65. Graduate of Northwestern University Medical School, Chicago, 1933. Licensed in California in 1941. Doctor Cooper was a member of the San Diego County Medical Society.

COPP, EDWARD F. FOSTER, La Jolla. Died 31 May 1969 in Borrego Springs of heart disease, aged 70. Graduate of University of Toronto Faculty of Medicine, Ontario, 1923. Licensed in California in 1926. Doctor Copp was a member of the San Diego County Medical Society.

✧

CRABTREE, ELMO GREGORY, San Diego. Died 5 June 1969 in San Diego, aged 68. Graduate of the University of Michigan Medical School, Ann Arbor, 1926. Licensed in California in 1927. Doctor Crabtree was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✧

CRANE, WALDO E., National City. Died 13 May 1969, aged 62. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1944. Licensed in California in 1944. Doctor Crane was a member of the San Diego County Medical Society.

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DAVIS, JOHN BENJAMIN, Long Beach. Died 1 May 1969 in Long Beach of adenocarcinoma of the prostate, aged 63. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1935. Licensed in California in 1937. Doctor Davis was a member of the Los Angeles County Medical Association.

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GOMSI, EDWIN S., Garden Grove. Died 11 May 1969 in Orange, aged 47. Graduate of the University of Minnesota Medical School, Minneapolis, 1947. Licensed in

California in 1952. Doctor Gomsí was a member of the Orange County Medical Association.



HOLM, BERNARD SANFRED, Richmond. Died 5 February 1969 in Richmond of cerebral hemorrhage, aged 65. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Doctor Holm was a member of the Alameda-Contra Costa Medical Association.



JOHNSON, RALPH MONTGOMERY, Woodland Hills. Died 3 May 1969 in Woodland Hills of arteriosclerotic cardiovascular disease, aged 78. Graduate of Harvard Medical School, Boston, 1918. Licensed in California in 1920. Doctor Johnson was a member of the Los Angeles County Medical Association.



LEAVELLE, ROBERT BRYAN, Van Nuys. Died 10 May 1969 in Burbank of subarachnoid hemorrhage, aged 52. Graduate of the University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1943. Doctor Leavelle was a member of the Los Angeles County Medical Association.



MANLEY, DONALD JAMES, Hayward. Died 15 May 1969 in Hayward of valvular heart disease, aged 70. Graduate of Creighton University School of Medicine, Omaha, 1923. Licensed in California in 1925. Doctor Manley was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.



PATTON, WILLIAM G., San Marino. Died 7 May 1969 in San Marino of lymphatic leukemia, aged 81. Graduate of Vanderbilt University School of Medicine, Nashville, Tenn., 1910. Licensed in California in 1936. Doctor Patton was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



POTTER, RALPH HUBERT, JR., San Francisco. Died 20 May 1969 in San Francisco, aged 48. Graduate of the University of Rochester School of Medicine, Rochester, N.Y., 1946. Licensed in California in 1952. Doctor Potter was a member of the San Francisco Medical Society.



PROCTOR, EDWARD ROSS (E. ROSS), Pomona. Died 1 May 1969, aged 72, of heart disease aboard his yacht

between Newport Beach and San Diego. Graduate of Columbia University College of Physicians and Surgeons, New York City, 1922. Licensed in California in 1943. Doctor Proctor was a member of the Los Angeles County Medical Association.



SCHARLES, FREDERICK H., Los Angeles. Died 1 June 1969 in Los Angeles of cerebral arteriosclerosis, aged 64. Graduate of Washington University School of Medicine, St. Louis, 1929. Licensed in California in 1947. Doctor Scharles was a member of the Los Angeles County Medical Association.



SPOONER, PHILIP F., Los Angeles. Died 29 May 1969 in La Canada of heart disease, aged 59. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1932. Licensed in California in 1932. M.D. degree from California College of Medicine, 1962. Doctor Spooner was a member of the Los Angeles County Medical Association.



STEIN, JACK LORENZ, Berkeley. Died 17 May 1969 in Berkeley of hypertensive and arteriosclerotic heart disease, aged 73. Graduate of the University of California Medical School, Berkeley-San Francisco, 1924. Licensed in California in 1924. Doctor Stein was a member of the Alameda-Contra Costa Medical Association.



THURLOW, ALFRED A., Santa Rosa. Died 19 January 1969 of coronary artery occlusion, aged 84. Graduate of the University of Michigan Medical School, Ann Arbor, 1909. Licensed in California in 1920. Doctor Thurlow was a retired member of the Sonoma County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



WALLER, LORENZ MCBURNEY, Hollywood. Died 28 May 1969 in Burbank of heart disease, aged 66. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1929. Licensed in California in 1933. Doctor Waller was a member of the Los Angeles County Medical Association.



WYMAN, BERYLE EDWARD, Los Banos. Died 23 April 1969 in a plane crash on the southeast slope of Red Slate Mountain near Bishop, aged 48. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1954. Licensed in California in 1955. Doctor Wyman was a member of the Merced County Medical Society.

WHAT IS FAMILY PRACTICE?



MANPOWER—NEW AIDES TO THE PHYSICIAN



SYSTEMS OF DELIVERY FOR HEALTH CARE SERVICES

THESE ARE THE TOPICS OF THREE GENERAL MEETINGS AT THE

1970 ANNUAL SCIENTIFIC ASSEMBLY

OF THE CALIFORNIA MEDICAL ASSOCIATION

SAN FRANCISCO, MARCH 7-11

THE NINETEEN SCIENTIFIC SECTIONS WILL ALSO HAVE
PROGRAMS ON A VARIETY OF SUBJECTS

◀ NEW MATERIAL SOLICITED ▶

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**PRESENTATIONS ARE NOT LIMITED TO THE SUBJECTS OF THE
GENERAL MEETINGS**

To Present a Paper

If you have a paper you'd like to present to your colleagues during their section meeting . . . write today to your section secretary (names and addresses of scientific section officers may be found on page 6, Advertising Section of *California Medicine*).

For Motion Pictures or Exhibits

If you have a motion picture or exhibit . . . write to the California Medical Association Committee on Scientific Assemblies, 693 Sutter Street, San Francisco 94102, for application forms.

PLANS FOR THE 1970 ANNUAL SCIENTIFIC ASSEMBLY ARE NOW IN PROGRESS

PLAN **YOUR** CONTRIBUTION TO THE PROGRAM **TODAY**

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Postgraduate Course Information

CMA:	California Medical Association For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
LLU:	Loma Linda University For information contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
PMC:	Pacific Medical Center For information contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
STAN:	Stanford University For information contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5940.
UCD:	University of California, Davis For information contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0333.
UCI:	University of California — California College of Medicine, Irvine For information contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
UCLA:	University of California, Los Angeles For information contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
UCSD:	University of California, San Diego For information contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
UCSF:	University of California, San Francisco For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
USC:	University of Southern California For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

CANCER

September 20—**Current Concepts in Cancer.** UCSF at Children's Hospital, San Francisco. Saturday.

September 26-27—**Cancer: Concepts and Controversy—Fifth Annual Cancer Symposium.** American Cancer Society, Sacramento Branch and California Division, UCD and CRMP Area II at Sahara Tahoe Hotel, Stateline, Nevada. Friday-Saturday. Contact: Richard K. Wertz, M.D., Symposium Chairman, 916 11th St., Sacramento 95814. (916) 446-7933.

September 26-27—**Current Concepts in Medical Oncology.** Medical Oncology Service, Mt. Zion Hospital and Medical Center at Mt. Zion Hospital, San Francisco. Friday-Saturday. Contact: Ernest H. Rosenbaum, M.D., Director, Medical Oncology Service, Mt. Zion Hospital and Medical Center, 1600 Divisadero, San Francisco 94115. (415) 567-6600. \$30.

October 4—**American Cancer Society, California Branch—Annual Scientific Program** at Hilton Inn, San Diego. Saturday. Contact: Forrest Willet, M.D., Medical Director, ACS, Calif. Div., 875 O'Farrell, San Francisco 94109. (415) 885-5822.

October 17-18—**Preoperative and Postoperative Radiation Therapy in the Treatment of Cancer—Fifth Annual San Francisco Cancer Symposium.** Zellerbach Saroni Tumor Institute and Dept. of Surgery, Mount Zion Hospital and Medical Center at St. Francis Hotel, San Francisco. Friday-Saturday. Contact: Mrs. Barbara Reynolds, Symposium Sec., Mt. Zion Hospital, 1600 Divisadero, San Francisco 94115. (415) 922-3823. \$40.

November 15-16—**Fifth Annual Clinical Cancer Conference.** UCSF. Saturday-Sunday.

December 7—**California Tumor Tissue Registry—Semi-Annual Cancer Conference.** Beverly Hilton Hotel, Beverly Hills. Sunday. Contact: W. K. Bullock, M.D., Exec. Dir., Los Angeles County Hospital, 1200 N. Lake St., Los Angeles 90033.

MEDICINE

August 16—**Electrocardiography.** PMC. Saturday.

August 17-20—**Advanced Seminars in Internal Medicine.** UCLA at Lake Arrowhead. Sunday-Wednesday. \$125.

August 25-29—**American Physiological Society.** Davis. Monday-Friday. Contact: Ray G. Draggs, Ph.D., Exec. Sec.-Treas., 9650 Rockville Pike, Bethesda, Md. 20014.

August 26-Sept. 1—**Pacific Dermatological Association.** Princess Kalulana Hotel, Honolulu. Tuesday-Monday. Contact: John M. Shaw, M.D., Sec.-Treas., 419 South L Street, Tacoma, Wash. 98405.

September 9-10—**19th Annual Professional Symposium on Cardiovascular Diseases.** San Diego County Heart Association in cooperation with USC at Hilton Inn, San Diego. Contact: James E. Lasry, M.D., Symposium Chairman, 3330 - 3rd Avenue, San Diego 92103.

September 13-19—**American Electroencephalographic Society.** El Cortez Hotel, San Diego. Saturday-Friday. Contact: Philip T. White, M.D., 8700 W. Wisconsin Ave., Milwaukee 53226.

September 14-20—**International Congress of Electroencephalography & Clinical Neurophysiology.** El Cortez Hotel, San Diego. Sunday-Saturday. Contact: Richard D. Walter, M.D., Congress Sec. UCLA.

September 20—**13th Annual Symposium on Cardiovascular Disease.** Ventura and Santa Barbara Counties Heart Associations at Biltmore Hotel, Santa Barbara. Saturday 9-5:00. Contact: Santa Barbara County Heart Assoc., 18 La Arcada Court, Santa Barbara 93104. (805) 963-1541. \$15.

September 26-28—**Diseases of the Colon and Anorectum.** UCLA at Wadsworth V.A. Hospital, Los Angeles. Thursday-Saturday.

September 27—**Lesions of the Mouth.** PMC. Saturday.

September 29 - Oct. 10 — **Intensive Review of Internal Medicine.** USC. Monday-Friday, Two weeks. \$150.

October 1-3 — **Annual Postgraduate Symposium on Heart Disease.** St. Francis Hotel, San Francisco. Wednesday-Friday. Contact: Gene C. Taylor, Executive Director, San Francisco Heart Assoc., 259 Geary Street, San Francisco 94102. (415) 982-5753.

October 1-3—**Respiratory Disease: Physiological Basis of Diagnosis and Treatment — 6th Annual Postgraduate Course on the Evaluation of Pulmonary Function.** TB and Respiratory Disease Association of California at UCLA. Wednesday-Friday. Contact: TB and Respiratory Disease Assoc. of California, 424 Pendleton Way, Oakland 94621. (415) 636-1756.

October 3-4—**Pulmonary Disease in Childhood.** Children's Hospital of Orange County, Orange. Friday-Saturday. Contact: William Taylor, M.D., Program Coordinator, Orange County Medical Center, 101 Manchester Avenue, Orange.

October 7 — **Evening Lectures in Medicine.** UCSF at Oakland Hospital. Tuesday evenings through Dec. 2.

October 10-12—**California Society of Internal Medicine—Scientific Program.** Coronado. Friday-Sunday. Contact: Cynthia Bell, Exec. Sec., 350 Post Street, San Francisco 94108. (415) 362-1548.

October 18—**Arrhythmias.** PMC. Saturday.

October 23—**Hypertension.** USC at Hilton Hotel, Los Angeles. Thursday.

October 29-30—**Symposium of Diabetes.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday.

October 31 — **Endocrinology — 14th Annual Medical Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals. Friday. Contact: Shirley Gach, Symposium Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027.

November 7-8—**Physical Medicine and Rehabilitation.** UCSF. Friday-Saturday.

November 8-9—**Manipulative Medicine.** USC. Saturday-Sunday. \$50.

November 13—**Office Dermatology.** USC. Wednesday.

November 13-15—**West Coast Allergy Society.** Hilton Inn, San Diego. Thursday-Saturday. Contact: Betty J. Jones, Exec. Sec., P.O. Box 42067, Portland, Ore. 97242.

November 15—**Gastroenterology.** PMC. Saturday.

Grand Rounds—Medicine

Tuesdays

9-10:30 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Wednesdays

Grand Rounds in Internal Medicine. 10:30-12:00 noon. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

Grand Rounds in Internal Medicine. 1:30-3:00 p.m., Fresno General Hospital.

Thursdays

10:30-12:00 noon, Room C3-105, UCLA Medical Center. UCLA.

Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

2-3:00 p.m., Classroom, Third Floor, Fresno General Hospital, Fresno. CRMP Area IV.

Rheumatology Grand Rounds. 11:30 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

OBSTETRICS AND GYNECOLOGY

August 13-17—**Second Annual Advanced Seminars in Obstetrics and Gynecology.** UCLA at Lake Arrowhead. Wednesday-Sunday. \$135.

September 25-27 — **The Office Practice of Ob/Gyn.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

December 5-6—**Obstetrics & Gynecology.** PMC. Friday-Saturday.

PEDIATRICS

September 19-20—**Pediatric Annual Meeting—Medical Staff, Children's Hospital, Oakland.** Highland Inn, Carmel. Friday-Saturday. Contact: Miss Inetta Carty, Children's Hospital, 51st and Grove Streets, Oakland 94609. (415) 654-5600.

September 24-25—**26th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Kenneth O. Williams, M.D., Sec.-Treas., P.O. Box 2022, Inglewood 90305.

September 27-28—**Pediatric Neurology.** UCLA. Saturday-Sunday.

September 29-Oct. 10—**Mental Retardation Workshop.** UCLA. Monday-Friday, Two weeks.

October 4-5—**Pediatric Neurology.** UCLA. Saturday-Sunday.

October 6-10—**Pediatric Allergy.** UCSF. Monday-Friday.

October 15—**Newborn Infant Care.** USC. Wednesday.

November 8-9—**Pediatric Neuroradiology.** UCLA. Saturday-Sunday.

November 10-12—**The Fetus and the Newborn.** American Academy of Pediatrics at UCSF. Monday-Wednesday. Contact: William H. Tooley, M.D., 327 Crestmont Dr., San Francisco 94131. (415) 566-7637.

Grand Rounds—Pediatrics

Tuesdays

8:30-9:30 a.m., Sixth Floor Conference Room, Harbor General Hospital, Torrance. UCLA.

8:30 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Conference Room, Sixth Floor, Harbor General Hospital, Torrance. CRMP Area IV.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and the Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Stanford University Medical Center, Palo Alto.

PSYCHIATRY

September 27-28—**Schizophrenia—Disease, Syndrome, or a Way of Life?** UCSF at Mendocino. Saturday-Sunday.

October 4-5 and 11-12—**Intermediate Methods in Family Therapy.** UCSF and San Joaquin County Mental Health Services at Stockton. Saturday-Sunday.

October 7—**Psychiatry and Civil Law.** UCLA. Tuesdays through Dec. 9.

October 18-19 — **Adscititious Therapies in Psychiatry.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday.

October 20-24—**Group Therapy.** UCSF at V.A. Hospital, San Francisco. Monday-Friday.

October 28-Nov. 2—**American Society of Clinical Hypnosis—12th Annual Scientific Meeting and Workshop.** Jack Tar Hotel, San Francisco. Tuesday-Sunday. Contact: F. D. Nowlin, Exec. Sec., 800 Washington Ave., S.E., Minneapolis 55414.

November 1—**The Context of Marriage.** UCSF. Saturday.

November 1-2—**The Problem of Alcoholism.** UCSF at Mendocino. Saturday-Sunday.

November 11-16—**Society for Clinical and Experimental Hypnosis—21st Annual Meeting.** Stanford Uni-

versity, Palo Alto. Tuesday-Sunday. Contact: Mrs. Mario Kenn, Society for Clinical and Experimental Hypnosis, 353 W. 57th St., New York 10019.

November 15-16—**Modern Theories in Psychiatry.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

December 6-7—**Therapy in Groups.** UCSF at Mendocino. Saturday-Sunday.

December 13-14—**Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton. Saturday-Sunday.

SURGERY

August 1-3 — **Monitoring the Anesthetized Patient—Current Trends.** UCLA. Friday-Saturday. \$65.

August 21-23—**Retinal Detachment Conference.** PMC. Thursday-Saturday. \$125.

September 4-6—**Scoliosis Research Society.** Disneyland Hotel, Los Angeles. Thursday-Saturday. Contact: William J. Kane, M.D., Sec.-Treas., Box 484, University Hospitals, Minneapolis 55455.

September 8 — **Spine Mechanics—Orthopedic Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals. Statler Hilton Hotel, Los Angeles. Monday, 2-5:30 p.m. Contact: Shirley Gach, Symposium Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027.

September 13—**Hand Injuries.** PMC. Saturday.

October 3-4—**Vascular Surgery.** UCSF. Friday-Saturday.

October 4—**Ophthalmology.** PMC. Saturday.

October 6-10—**American College of Surgeons—Annual Meeting.** Fairmont Hotel, San Francisco. Monday-Friday. Contact: John Paul North, M.D., 55 E. Erie Street, Chicago 60611.

October 14-22—**Pan-Pacific Surgical Association.** Hawaiian Hilton, Honolulu. Tuesday-Wednesday. Contact: Mrs. Harriet N. DeVault, Exec. Sec., Rm. 236, Alexander Young Bldg., Honolulu 96813.

October 25-29—**American Society of Anesthesiologists—Annual Session.** Hilton Hotel, San Francisco. Saturday-Wednesday. Contact: John W. Andes, Exec. Sec., 515 Busse Highway, Park Ridge, Ill. 60068.

October 31-Nov. 1—**Surgical Emergencies.** PMC. Friday-Saturday.

December 4-6—**Management of Uveitis—Annual Proctor Foundation Program.** UCSF. Thursday-Saturday.

December 12-14—**Fluid & Electrolytes.** USC at Palm Springs. Friday-Sunday.

Grand Rounds—Surgery

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

9:30 a.m., Neuroradiology, 10:15 Neurology, 11:15 Neurosurgery. Stanford University Medical Center, Palo Alto.

Saturdays

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

OF INTEREST TO ALL PHYSICIANS

August 10-14—**National Medical Association.** Hilton Hotel, San Francisco. Contact: John T. Givens, M.D., Exec.-Sec., 2400 Corprew Avenue, Norfolk 23504.

August 16-27—**12th Annual Postgraduate Refresher Course.** USC at Honolulu and Maui, Hawaii. Saturday-Wednesday.

September 18-20—**Annual Postgraduate Assembly—Birth Defects.** St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: John C. Eagan, M.D., Director, St. John's Hospital Postgraduate Assembly, 1328 22nd St., Santa Monica 90404.

September 24—**Clinical Psychiatry for Non-Psychiatrists: A Course in Medical Psychotherapy.** UCSF. Wednesdays through Dec. 17.

September 25-27—**Initial Emergency Care.** UCSF and American Association of Orthopedic Surgeons. Thursday-Saturday.

October 2—**A Course in Mental Retardation for Physicians.** UCSF. Thursdays through May 21.

October 9 - Nov. 13—**Freedom of Choice.** UCSF. Thursday evenings.

October 11-12—**Health of the School Child.** UCSF. Saturday-Sunday.

October 11-12—**Kern Postgraduate Conference.** Kern County General Hospital at Civic Auditorium, Bakersfield. Saturday-Sunday. Contact: George A. Paulsen, M.D., Conference Committee Chairman, 2603 G St., Bakersfield 93301. (805) 327-7637.

October 17-18—**Thirteenth Annual Western Industrial Health Conference.** Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Mr. B. H. Bravinder, 2180 Milvia St., Berkeley 94704.

October 17-18—**Western Industrial Medical Association.** Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Mr. B. H. Bravinder, 2180 Milvia St., Berkeley 94704.

October 24-25—**Recreation in Rehabilitation.** UCSF. Friday-Saturday.

October 25-26—**How the Patient Affects the Doctor.** UCSF at Fresno Community Hospital, Fresno. Saturday-Sunday.

November 2-5—**California Academy of General Practice—21st Annual Scientific Assembly.** Century Plaza Hotel, Los Angeles. Sunday-Wednesday.

November 15—**Mayo Alumni Association—45th Annual Meeting.** Century-Plaza Hotel, Los Angeles. Saturday. Contact: Office of the 45th Annual Meeting, 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

November 15-16—**Financial, Tax and Investment Planning.** UCLA. Saturday-Sunday.

November 15-16—**Sex and the Professional Man.** Christian Medical Society at Monte Corona Conference Grounds, Lake Arrowhead. Saturday-Sunday. Contact: Albert Holt, M.D., 4080 Hoking Way, Los Angeles 90027.

December 3—**Postgraduate Assembly—St. Luke's Hospital of Pasadena.** At the Huntington-Sheraton Hotel, Pasadena. Wednesday. Contact: W. K. Bullock, M.D., Chairman, 1969 Postgraduate Assembly, 2632 E. Washington Blvd., Pasadena 91107.

CONTINUOUSLY

Basic Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

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BOOK REVIEWS

MARIJUANA — E. R. Bloomquist, M.D., The Glencoe Press (A Division of the Macmillan Company), 8701 Wilshire Blvd., Beverly Hills, Calif. (90211), 1968. 215 pages, \$1.25 (Paperback).

These days it is incumbent upon every practicing physician to inform himself about *cannibis sativa* whether the variety be *indica*, *americana* or *mexicana*. Dr. Bloomquist's readily readable and widely ranging review provides most of what one needs to know—except perhaps the *smell* of burning "pot"! Marijuana is considered in terms of its easy cultivation almost anywhere in the world and the long history of its use to produce clothing, rope and psychedelic bliss. There is discussion of the current drug "scene" and of the background of the present controversy concerning whether or not the use of marijuana is harmful either to the individual user or to society as a whole. The problems of the teen-age experimenter and the pusher and the law are reviewed with comment.

The book, a paperback, is written by one who knows the subject well and it serves admirably to orient the "square" physician to problems he may expect to encounter sooner or later in his practice, if indeed not in his home. It is too bad that the only illustration of the plant to be found in the book dates from the first century after Christ!

M. S. M. WATTS, M.D.

* * *

MEDICAL HISTORY FOR STUDENTS — John R. Green, M.D., Chairman, Barrow Neurological Institute, St. Joseph's Hospital, Phoenix, Ariz., Lecturer, Department of Zoology, History of Medicine, Arizona State University, Tempe, Ariz. Charles C Thomas, Bannerstone House, 301-327 East Lawrence Ave., Springfield, Ill. (62703), 1968. 197 pages, \$9.75.

It is interesting to note that with almost inverse proportionality to the relative decrease in the teaching of the history of medicine in schools of medicine there has been a growing interest in the presentation of the subject as part of the general history of culture to undergraduates and high school students. In recent years, a number of courses have arisen in various colleges and universities and correspondingly short texts in the history of medicine have made their appearance to meet the need. The present text is just such a work. It has evolved from a course given to undergraduate and graduate students at Arizona State College but, as stated in the preface and on the dust-sheet, the book was composed with more ambitious aims and a broader audience in mind "to widen the horizon of general education, to form the foundation for professional knowledge and, fortifying it, to stimulate further study of medical history."

The text follows conventional lines proceeding from primitive and archaic medicine, through the Greco-Roman period, Arabic and Medieval medicine to the Renaissance, thereafter taking up seriatim the progress

made in each century to the twentieth. Nevertheless this is all done in some 177 pages if we exclude the preface, reading list, and index, which is quite a triumph of condensation and surprisingly is, by and large, a well balanced presentation. But in achieving brevity it inevitably suffers in style and conceals in dogmatic and orthodox statements much that is highly controversial. For example, Imhotep is called "a master of medicine" (p. 13) and it is said (p. 15) that his concepts and practices were recorded on papyri one of which "is actually the most important and complete treatise on surgery of all antiquity . . . discovered at Luxor by Edwin Smith in 1862." Such statements, apparently derived from the *speculations* of Professor Breasted, the translator of the Smith Papyrus, are totally without documentary support. Tradition only binds Imhotep to medicine. A thousand years were to elapse (New Empire) before he became a demi-god, and 25 centuries (Saite period) before he was ranked as a god under the title son of Pthah and of Sekhmet, patron of medicine. Similarly we are told categorically (p. 37) that the Etruscans were Hittite invaders who carried with them hepatoscopy as evidenced by the so-called Piacenza liver. However, there is perhaps no more complicated question than the origin of the inhabitants and the cultural overlays of Etruria — Apenninic, Villanovan, Lydian, *Twrws.w* (Turusha), Greek, Chaldean — a case can be made for all, but in recent years the autochthonic theory, that Etruscans are native to Etruria with several secondary cultural overlays, has gained in popularity. There is evidence that the Piacenza as well as the Falerii liver, together with a bronchoscopic calendar based on the liver, were introduced late by Chaldeans who travelled in Italy in the days of Cato and are not evidence of ethnic origins. The reader should be aware of the ambiguities which are many, due doubtless to excessive compression, and of a number of errors of fact such as the date of founding of the University of Edinburgh given in Figure 18 as 1685 (date of the medical school) instead of 1583; the annexation of temples to Sais in 4000 B.C. (p. 19); the description of Estienne's book (p. 73); John Caius as a student of Vesalius (p. 82) which he was not; and several more which will doubtless receive correction in later editions.

The author has done very well in relating the development of medicine to contemporary events considering the small amount of space he has allotted to himself to tell a story which reaches into almost every land and culture over many millenia. Despite its imperfections and the absence of any discussion of biochemistry (the word or its variants do not even appear in the index), the work fulfills very well the needs of the audience to which it is directed as a good introductory text on the history of medicine.

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References and Reviews

Science, Washington

Transplacental Hemorrhage in Spontaneous and Induced Abortion—C. D. Matthews (West Middlesex Hosp., Isleworth, England) and A. E. B. Matthews, *Lancet* 1:694-695 (April 5) 1969.

In a series of 387 patients the Kleihauer technique was used to identify fetal red blood cells within the maternal circulation following spontaneous abortion and termination of pregnancy. The incidence of transplacental hemorrhage for spontaneous abortion was about 6 percent; but no significant hemorrhage (over 5 cells/100 lpf) was noted in the 166 cases studied. The vaginal (118) and abdominal (103) termination of pregnancy presented a different picture. Approximately 25 percent showed evidence of transplacental hemorrhage, which in 3 percent of cases reached or exceeded the amount suggested as potentially immunizing (25 cells/100 lpf). There was no difference in the incidence or degree of transplacental hemorrhage between termination by the vaginal or abdominal route.

(Continued on page 42)

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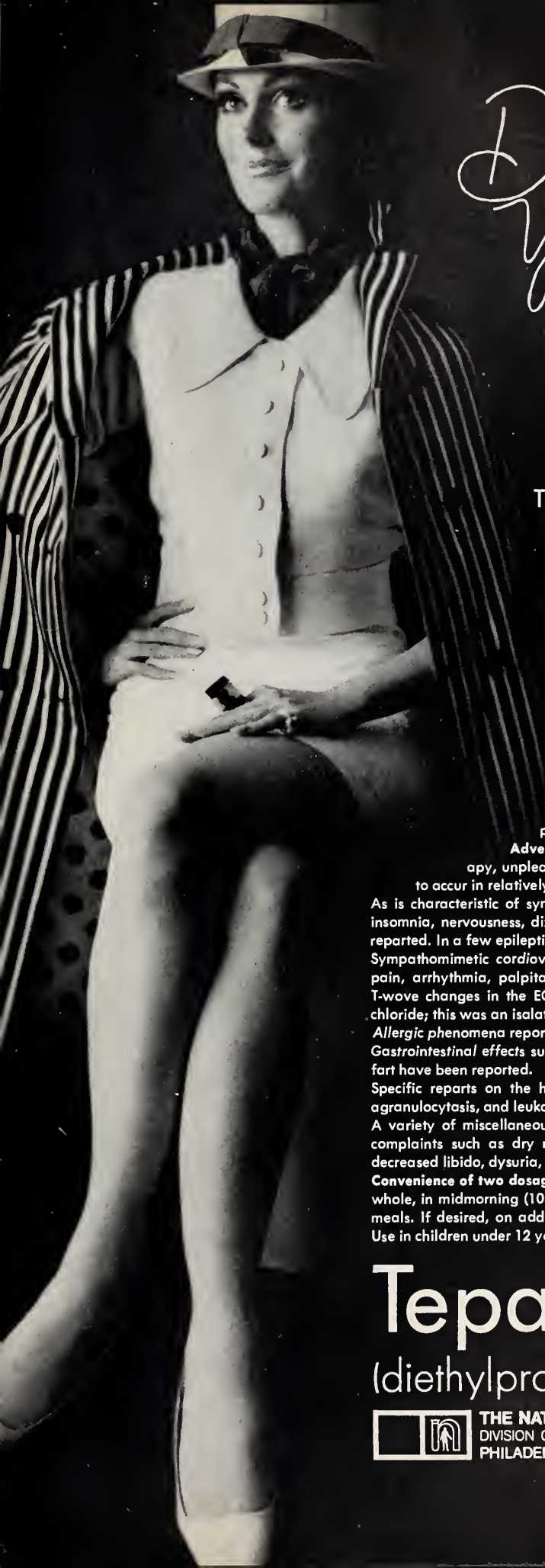
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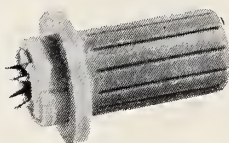
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(Continued from page 38)

Hospital Facilities for Children — H. S. Thorpe (805 Oak Ave., Davis, Calif.) and **P. Rousseau, Amer. J. Dis. Child.** 117:558-565 (May) 1969.

Current standards for pediatric hospital care include meeting the child's emotional needs. To compare these standards with actual practice, a survey of six regional hospitals was undertaken. Most members of the pediatric, nursing, and supportive staff of these institutions were skillful in and empathetic with the needs of sick children and their families. Increased use of informational booklets and pediatric preadmission visits were recommended. Layout and location of pediatric units often evidenced architectural inadequacies. They adjoined adult wards, were noisy, lacked safety features, and were inadequately staffed. Overnight facilities for parents were generally limited and their use not encouraged. Nonteaching hospitals lacked effective supportive and volunteer staff, whereas teaching units placed varying emphasis on psychiatric liaison, consultation, and multidisciplinary management groups in pediatric departments.

PHYSICIANS WANTED

(Continued from page 24)

THORACIC SURGICAL TREATMENT RESIDENCY — Unexpected opening in approved Thoracic Surgical Residency. Requirements include three years of approved General Surgical Residency and a California State License. Olive View is an 800 bed County hospital, 25 miles from the center of Los Angeles. Please contact Joseph K. Indenbaum, M.D., Medical Director, Olive View Hospital, Olive View, Calif. 91330. (213) 367-2231 Ext. 388.

OLIVE VIEW HOSPITAL, a unit of Los Angeles County Hospital System. Openings for Board-eligible or certified internists to participate in developing acute and chronic medical service. Salary begins at \$20,628 plus liberal County fringe benefits. For a modest amount of night and weekend coverage, the total salary should increase to \$28,000. California State License is required. Interested physicians should contact Joseph K. Indenbaum, M.D., Medical Director, Olive View Hospital, Olive View, Calif. 91330.

GENERAL PRACTITIONER. 14-man group. No obstetrics or major surgery. Salary \$2,000 plus percentage. Hofgaarden Medical Center, 711 W. Valley Blvd., Alhambra, Calif. 91803.

INTERNIST. Group practice—14-man group. Regular hours. No night calls. Salary \$2,000 plus percentage. Hofgaarden Medical Center, 711 W. Valley Blvd., Alhambra, Calif. 91803.

OBSTETRICIAN-Gynecologist — Opportunity in a small smog-free coastal area., Boards or eligible, in a fourteen-man specialty group. Excellent hunting and fishing, good schools and living environment. Contact Administrator, San Luis Medical Clinic, 1235 Osos Street, San Luis Obispo, California 93401.

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GENERAL SURGEON, Pediatrician, Radiologist, Pathologist, Board certified or eligible, wanted by 10-man multispecialty group. Pleasant college community of 15,000; modern clinic and new 120-bed hospital; liberal fringe benefits; salary negotiable. Contact: Administrator, DePuy-Sorkness Clinic, 401 Third Street Southeast, Jamestown, North Dakota 58401.

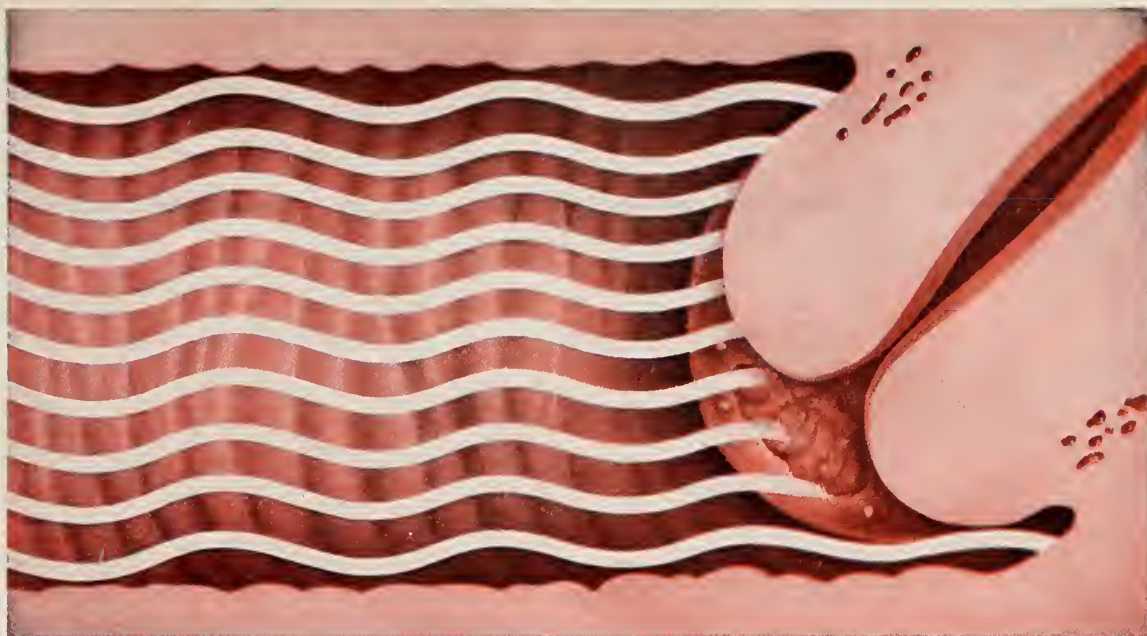
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OBS-GYN Suburban area So. Calif. Diplomate needs Assoc. guar. and percentage leads to partnership. Inland nr. San Diego Diplomate needs assoc. \$24,000 to partnership. Nr. San Francisco Diplomate offers space and referrals to specialists OBS-GYN wanting own practice. **CONTINENTAL PACIFIC COAST MEDICAL AGENCY**, 9777 Wilshire, Beverly Hills, Calif. 90212.

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(Continued on page 46)



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BOOKS RECEIVED

Books received by CALIFORNIA MEDICINE are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.

THE EVOLUTION OF PREVENTIVE MEDICINE IN THE UNITED STATES ARMY, 1607-1939—Stanhope Bayne-Jones, M.D., Brigadier General, USAR, Retired, Deputy Chief, Preventive Medicine Service, Office of the Surgeon General, in World War II; Prepared and published under the direction of Lieutenant General Leonard D. Heaton, Surgeon General, United States Army. Office of the Surgeon General, Department of the Army, Washington, D.C., (1968). 255 pages, including three appendixes, 39 illustrations, \$2.50.

PULMONARY EMPHYSEMA AND RELATED LUNG DISEASES—Theodore Rodman, M.D., Associate Professor of Medicine, Temple University School of Medicine; and Francis H. Sterling, M.D., Associate in Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa. C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1969. 468 pages, 294 illustrations, \$27.50.

TEXTBOOK OF IMMUNOPATHOLOGY—Peter A. Miescher, Professor of Hematology; Head, Division of Hematology, Hospital Cantonal, University of Geneva, Geneva, Switzerland; and Hans J. Muller-Eberhard, M.D., Member, Scripps Clinic and Research Foundation, Department of Experimental Pathology, La Jolla, California and Professor of Pathology in Residence, University of California at San Diego, La Jolla, California; with 75 contributors. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. Volume I, 384 pages, \$19.75. Volume II, 420 pages, \$24.75.

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ANATOMY—A Regional Study of Human Structure—Third Edition—Ernest Gardner, M.D., Wayne State University; Donald J. Gray, Ph.D., Stanford University; and Ronan O'Rahilly, M.Sc., M.D., Saint Louis University; Illustrated by Casper Henselmann, W. E. Saunders Company, West Washington Square, Philadelphia, Pa. (10105), 1969. 549 figures on 67 plates, 812 pages, \$19.00.

ANNUAL REVIEW OF MEDICINE—Volume 20—Arthur C. DeGraff, Editor, New York University School of Medicine; and William P. Creger, Associate Editor, Stanford University School of Medicine. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, Calif. (94306), 1969. 499 pages, \$8.50.

MEDICAL DEPARTMENT, UNITED STATES ARMY—MEDICAL SUPPLY IN WORLD WAR II—Prepared and published under the direction of Lt. Gen. Leonard D. Heaton, the Surgeon General, United States Army; Editor in Chief, Col. Robert S. Anderson, M.C., USA; Editor for Medical Supply, Charles M. Wiltse, Ph.D., Litt.D., Office of the Surgeon General, Department of the Army, Washington, D.C. (1968). 149 illustrations, 54 maps, 8 tables, comprehensive index, \$8.25 per copy from the Superintendent of Documents, Government Printing Office, Washington, D.C. (20402). 662 pages.

MOTOR NEURON DISEASES—Research on Amyotrophic Lateral Sclerosis and Related Disorders—Contemporary Neurology Symposia, Volume II—Edited by Leonard T. Kurland, Rochester, Minn.; and Forbes H. Norris, Jr., San Francisco. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 407 pages, \$13.25.

ON DEATH AND DYING—Elisabeth Kübler-Ross, M.D. The Macmillan Company, Collier-Macmillan Ltd., 866 Third Avenue, New York (10022), 1969. 260 pages, \$6.95.

PROGRESS IN CLINICAL PSYCHOLOGY—Volume VIII—Dreams and Dreaming—Edited by Lawrence Edwin Abt, Ph.D.; and Bernard F. Riess, Ph.D. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 192 pages, \$9.75.

SURGERY OF THE CHEST—Second Edition—With the Collaboration of 48 Authorities—Edited by John H. Gibbon, Jr., M.D., formerly Samuel D. Gross Professor of Surgery and Chairman of the Department of Surgery, The Jefferson Medical College, Philadelphia; David C. Sabiston, Jr., M.D., Professor and Chairman, Department of Surgery, Duke University School of Medicine, Durham, N.C.; and Frank C. Spencer, M.D., George David Stewart Professor of Surgery and Chairman of the Department of Surgery, New York University School of Medicine, New York, N.Y. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 954 pages, \$32.50.

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A Tranquilizer-Anticholinergic Preparation in Functional Gastrointestinal Disorders: A Double-Blind Evaluation

HOWARD H. WAYNE, M.D., *San Diego*

■ *Chlordiazepoxide plus clidinium bromide (Librax[®]) was evaluated and compared with a placebo by means of a random sample, double-blind crossover technique in 42 patients presenting ordinary functional gastrointestinal disorders.*

Results:

- *73.9 percent excellent-to-good response to the active drug in patients receiving it before they received the placebo, compared with 44.5 percent in those who did not receive it until after the placebo period.*
- *58.9 percent excellent-to-good response to the active drug in patients who received it after the placebo period, as compared with 31.8 percent in those receiving the placebo last.*
- *Overall clinical response 67.5 percent excellent-to-good with the active drug as compared with 37.5 percent with the placebo.*
- *Excellent-to-good results in 12 follow-up patients receiving the known active drug.*
- *Statistically significant symptomatic response in four of eight target symptoms.*

The tranquilizer-anticholinergic preparation used appeared to improve not only patient outlook and attitudes but to effectively relieve both the physiologic and psychic manifestations of common functional gastrointestinal disorders.

THAT EMOTIONS EXERT a distinct and widely recognized effect on somatic activity is hardly a new concept. Plato is quoted as saying: "For this is the great error of our day . . . that physicians

separate the soul from the body." In no area is there more evidence of altered function caused by emotional stress than in the gastrointestinal system. Sympathetic and parasympathetic nerves reach all parts of the digestive system regulating its motility, secretion and blood supply. Over 50 percent of the varied digestive tract complaints

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seen by physicians are quite clearly functional,¹ mainly resulting from disturbed motility. This is manifested by smooth muscle spasms or hyperperistalsis anywhere along the tract. The variety of complaints induced by these spasms is indeed impressive, ranging from functional indigestion to "irritable colon syndrome."

Ranking with the common cold as a leading cause of recurrent minor disability, irritable colon is a prime example of a disturbance associated with chronic emotional tension.² Common clinical symptoms are: abdominal pain of varying degree, constipation, gaseous distension of the proximal colon, flatus, diarrhea, nausea and, occasionally, vomiting. The knowledge that onset and recurrences of this syndrome usually coincide with periods of stress or conflict and disappear spontaneously with their abatement is fundamental to differential diagnosis.

The recognition of irritable colon and similar functional gastrointestinal disorders as reactions to stress calls for treatment directed to the patient as a whole, his attitudes and his environment. After the patient has been reassured that the illness is not organic, he should be encouraged to ventilate his feelings. The presenting symptoms should then be treated with suitable drugs. The oldest rationale consists of an anticholinergic drug to inhibit gastrointestinal motility together with a sedative or tranquilizing agent to deal with the extreme degrees of anxiety, insomnia and tension.

Preparations combining both agents have therefore been introduced and have been generally well received. One of the more widely used and clinically effective combinations consists of clidinium bromide and chlordiazepoxide.* Efficacy in clinical trials^{3,5} has ranged from 76 to 97 percent excellent-to-good response. Moreover, the value of each drug individually in the treatment of functional gastrointestinal disorders has been reported previously.⁶⁻¹⁰ It was therefore decided to undertake a controlled study of the effects of this combination and an identically appearing placebo, using a standard double-blind crossover technique.

Methods and Materials

Patient selection was based on the chronicity and duration of illness to rule out the possibility that symptoms of brief duration might subside spontaneously and be falsely attributed to the

TABLE 1.—*Patient Distribution in Double-Blind Study*

Age	No. of Pts.	Male	Female
19 - 29	5	..	5
30 - 39	6	4	2
40 - 49	16	6	10
50 - 59	8	5	3
60 - 69	5	2	3
70 - 75	2	1	1
Totals:	42	18	24
Average Age:	44.04 years		

medication. Forty-two patients were selected, all of whom had had gastrointestinal disorders ranging from six months to many years. There were 18 males and 24 females, aged 19 to 75 years (Table 1). The peak incidence occurred between 40 and 49 years and declined steadily thereafter.

Complete history was obtained from all patients, subjective symptoms were recorded, and physical and radiographic examinations were carried out. Gastrointestinal and gall bladder series were normal in all but two patients: gastroesophageal reflux was revealed in one, and a nonfunctioning of the gall bladder in the other. Patients with active ulcers were also excluded from the study because of jeopardy during the placebo-treatment period.

Five diagnostic categories were determined — functional indigestion (22 patients), irritable colon syndrome (four patients), pyrosis (two), pylorospasm (two), and a mixed group exhibiting more than one of the preceding disorders (12). Also included in the last category were patients with flatulence (one), gastrointestinal neurosis (one), postcholecystectomy syndrome (one), hiatus hernia (one) and gastroesophageal reflux (one). In many instance a variety of antacids, laxatives, analgesics and other medications had been tried without success. All previous therapy was discontinued before the controlled study was begun.

The eight most common presenting complaints (heartburn, nausea, emesis, flatulence, abdominal pain, diarrhea, anxiety-tension and insomnia) were selected as the target symptoms for evaluation before treatment and after both trial periods. These same symptoms were evaluated once again during the requested follow-up period with the active medication.

The test drug was supplied in capsule form, each containing 2.5 mg of clidinium bromide and 5 mg of chlordiazepoxide, in sufficient quantity to permit varying the dosage from one capsule daily to one four times daily for a minimum four-week period. Identical placebo capsules were provided

*Librax® Roche Laboratories, Division of Hoffmann-La Roche Inc., Nudely, New Jersey.

TABLE 2.—Drug Response by Order of Administration

	Total No. of Pts.	Dropped Out	Positive Response		Totals and Percent		Negative Response				Totals and Percent	
			E	G	No.	Percent	G-F	F	F-P	P	No.	Percent
GROUP I	23											
Chlordiazepoxide + Clidinium bromide			5	12	17	73.9		3	1	2	6	26.1
Placebo		1	4	3	7	31.8	1	1	3	10	15	68.2
GROUP II	19											
Placebo		1	2	6	8	44.5	1	3	1	5	10	55.5
Chlordiazepoxide + Clidinium bromide		2	6	4	10	58.9		1		6	7	41.1
OVERALL RESPONSE	42											
Chlordiazepoxide + Clidinium bromide		2	11	16	27	67.5		4	1	8	13	32.5
Placebo		2	6	9	15	37.5	2	4	4	15	25	62.5

E = excellent, G = good, F = fair, P = poor.

in similar amounts and both were sealed in separate envelopes coded for future identification and random order of administration. Initially the patients were instructed to take one capsule four times daily and to return after two weeks for evaluation. At the end of the four-week period (or sooner if the patient complained strongly of lack of response) the alternate crossover envelope was supplied. Upon completion of the study and breaking of the code numbers, patients were divided by order of drug administration into Group I (receiving the active medication initially) and Group II (receiving the placebo first). At the completion of both trial periods, follow-up treatment with the active drug was continued if the patient so requested.

Responses were graded as excellent (complete remission), good (partial remission), fair (slight improvement) and poor (unchanged). Wherever a definite response could not be determined, ratings were expanded to include "good-to-fair" and "fair-to-poor" categories.

Results

Clinical response. Response was reviewed both by order of drug administration and regardless of the order followed.

- Group I: Of 23 patients receiving clidinium bromide plus chlordiazepoxide as initial medication 17 (73.9 percent) showed a positive response to therapy in the excellent-to-good range—complete or partial remission of symptoms (Table 2). In contrast, only seven of twenty-two (one dropped out) or 31.8 percent had excellent-to-good response after crossover to placebos.

- Group II: The patients who received the

placebo medication initially had less impressive results. Eight of 18 (44.5 percent) of the placebo patients (one dropped out) had excellent-to-good response to placebos; and when the switch to active medication was made, ten of seventeen (two dropped out) or 58.9 percent had response of that order.

Note that Group I patients obtaining relief in the first trial did not necessarily find a similar improvement on placebo, since the response dropped to less than half (31.8 percent) in the second period. Four patients asked to be returned to the original medication because of treatment failure and two dropped out of the study.

Total clinical improvement tabulated for the 42 patients regardless of order of administration and taking into account the four patients who did not complete the study was highly indicative of active drug efficacy. Twenty-seven patients (67.5 percent) improved on the medication as compared with 15 (37.5 percent) on the placebo (Table 2). Negative responses on the placebo were almost twice the number occurring during therapy with the active drug (25:13).

Symptomatic response. Table 3 presents the effect on target symptoms as reported on the drug evaluation forms. Greatest improvement was noted in patients with insomnia, anxiety-tension, abdominal pain and nausea. These results also point up the greater alleviation of symptoms in patients receiving the active preparation initially (Group I). When the medication was used in the second trial period (Group II), the response was slightly lower, although it exceeded that noted with the placebo in both periods.

TABLE 3.—Symptomatic Response of Two Groups Compared with Pretreatment Levels

Target Symptom	Group I (23 patients)										Group II (19 patients)									
	Pretreatment					Active Drug					Placebo					Placebo				
Severity* —	3	2	1	0	DO	3	2	1	0	DO	3	2	1	0	DO	3	2	1	0	DO
Abdominal pain	7	9	3	4	1	8	14	1	8	7	6	1	6	7	3	3	..
Anxiety-tension	5	7	5	6	..	5	5	13	3	4	5	10	1	3	8	5	3	3
Diarrhea	1	2	2	18	..	1	..	22	1	21	1	1	2	3	13	..
Emesis	3	20	..	1	22	22	1	1	3	15
Flatulence	16	3	4	..	3	2	10	8	5	7	4	6	1	10	7	1	1	2
Heartburn	5	6	5	7	1	2	8	12	2	4	4	12	1	5	4	2	8	..
Insomnia	4	5	3	11	..	1	4	18	2	2	5	13	1	3	4	3	9	3
Nausea	..	9	3	11	..	1	2	20	3	2	2	15	1	4	3	6	6	1
Totals	38	41	28	77	5	12	38	129	16	27	28	105	8	32	36	26	58	9
Total No. Mild or No Symptoms	105					167					133					84				
																111				
																116				

*Severity ratings: 3 = severe, 2 = moderate, 1 = mild, 0 = none, DO = dropped out.

TABLE 4.—Side Effects Reported During Double-Blind Study

Side Effect	Following Active Drug (18 Patients)					Following Placebo (16 Patients)				
	Severe	Mod.	Mild	Mild	Total	Severe	Mod.	Mild	Mild	Total
Ataxia	2	1	3	2	2
Blurred vision	1	1	2	2	1	3
Constipation	1	4	5	..	1	1	4	6
Depression	1	1
Difficulty in urinating	1	1	2	1	2	3
Dizziness	1	1
Drowsiness	1	2	7	10	1	1	2	..
Dry mouth	1	3	2	7	13	5	5
Hoarseness	1	1
Nausea	1	1	..
Totals	1	5	8	23	37	..	1	5	17	23

Twelve patients requested continuation of treatment after the eight-week trial period was completed and were given chlorthalidone plus cimetidine bromide, regardless of the last drug administered. Diagnoses included functional indigestion (five cases), irritable colon syndrome (three), combination of both indications (two), anxiety colitis (one), and functional indigestion with gastrointestinal reflux (one). Excellent-to-good response was reported in ten patients (83.3 percent). The two patients with treatment failure were in the same diagnostic category — functional indigestion plus irritable colon syndrome. One of these was from Group II and had had poor results on the second trial with the active medication, which extended into the post-trial period. The second patient had had poor results with both test medications, and this continued throughout the follow-up period.

Side Effects. A total of 37 side effects were re-

ported in 18 patients on the combination, while 23 occurred in 16 patients following placebo therapy. Dry mouth and drowsiness were most frequently reported in the former group, and constipation and dry mouth accounted for the majority of disturbances in the placebo group (Table 4). A common result of anticholinergic therapy, dry mouth could be expected to a mild degree with cimetidine bromide administration, but its frequent occurrence in placebo-treated patients suggests a possible relationship to the anxiety-tension component of the disorder.

In four patients receiving the active drug and in two receiving the placebo as initial medication, side reactions improved either spontaneously or with minor dosage adjustment. Treatment was discontinued in four patients, in two following placebo therapy and in two after the active medication. In only one case was crossover therapy completed before drop-out.

Statistical Evaluation of Symptomatic Response. For purposes of statistical analysis, differences were determined between the symptomatic ratings made before and after therapy with both the active drug and placebo for each patient in whom treatment periods were approximately equivalent. The resulting "improvement scores" were then analyzed by means of a Student two-sample t-test of crossover data. Chlordiazepoxide plus clidinium bromide showed a highly significant difference ($P<.01$) in patients with insomnia, and a significant difference ($P<.05$) in patients with abdominal pain, anxiety-tension and nausea.

Discussion

The effectiveness of the test drug as compared with the placebo was clearly demonstrated in the patients who were given the drug as initial medication. A positive response was obtained in 73.9 percent, but dropped to 31.8 percent after placebo administration. Four patients who found the second medication ineffective requested a change back to the original drug.

It is well to bear in mind that the patients in this study had chronic disorders and had received previous therapy which had not proved satisfactory. Hence there was a general feeling of discouragement and pessimism, and this may have been reflected in the group receiving the placebo as initial medication. In that group a positive response was observed in 44.5 percent, and an increase of only 14.4 percent (to 58.9 percent) was obtained following the period of active drug administration. It is quite possible that initial treatment with the

placebo jeopardized subsequent results with the active medication by causing the patient to lose confidence in the therapy. The small difference between the response scores may indicate a psychological carryover effect from the first to the second trial period; in other words, the patients who did not react to the placebo also did not react to the active medication, possibly carrying over a feeling of failure to the second trial period.

Evaluation of the effect of chlordiazepoxide and clidinium bromide on target symptoms revealed the greatest effect on anxiety-tension, insomnia, abdominal pain and nausea, thus reflecting the combined tranquilizing-anticholinergic action of the medication. The advantage of such a combination over anticholinergic therapy alone is obvious for the treatment of tense, anxious and emotional patients with functional gastrointestinal disorders.

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—MARK M. MARKS, M.D., Kansas City

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Total Retropubic Prostatectomy

EVERETT D. HENDRICKS, M.D., BEN D. MASSEY, M.D.,
EARL F. NATION, M.D., CHARLES A. GALLUP, M.D., AND
BEN D. MASSEY, JR., M.D., Pasadena

■ *Results in 96 patients who had total retropubic prostatectomy were reviewed. The most common complications were impotence and difficulty with urinary control. The most serious were rectal injury and vesical neck contracture. Twenty-eight of 33 patients who were followed for five years after operation and eight of twelve who were followed for ten years were alive without evidence of recurrence of cancer. Evidence of recurrence was found only in patients in whom cancer had spread beyond the parenchyma of the prostate before operation. There were no operative deaths.*

FOR THE PATIENT with early prostatic carcinoma, we are without definite evidence for the superiority of any one method of treatment. The wide variation in survival with this disease, treated or untreated, makes evaluation of different types of treatment difficult. Conscious and unconscious selection of cases tends to make comparison of survival in reported series uncertain.

It is doubtful that unanimity of opinion can be reached until such time as a large number of similar patients, some treated surgically, some with hormones, and some with radiation, are followed for perhaps 15 or 20 years. In the meantime, it has been our belief that patients with localized prostatic cancer are better off having that cancer removed surgically, provided the hazards and complications of operation are not too great.

We reviewed the records of all the 96 private patients upon whom we had done total prostatectomy, to determine the extent of those hazards and complications and to judge whether the results justified the complications.

The average age of patients was 62.4 years; the youngest was 50, the oldest 73. We considered patients over 65 years for operation only when they were in better physical condition than the average person in the age group.

Diagnosis was made by needle biopsy, percutaneously, in 75 of the 96 patients. In 71 of the 75 cases one biopsy sufficed for diagnosis.

Twenty-one patients first had transurethral resection. In 16 of them, the diagnosis of carcinoma was not suspected until the tissue was examined histologically. In such cases we review the histologic picture carefully with the pathologist. If the lesion is grade I in degree of differentiation and seems to be well localized, without invasion, total prostatectomy is not considered. If the carcinoma is more active than grade I or is found in more than one localized area or is invasive, the patient is a candidate for ablative operation. This distinction is our attempt to distinguish the lethal from the indolent in these so-called occult carcinomas. In only one of the 16 patients was there evidence of recurrence after operation. We follow Goodwin's¹ method of staging these tumors (Table 1). With the exception of the 16 with occult carcinoma, we believed before operation in all cases that the tumor was a localized nodule (Stage A) or con-

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r Carcinoma of the Prostate

fined to a localized area of the parenchyma of one lobe (Stage B). All patients were given estrogen therapy as soon as the diagnosis was made. In four patients a lesion thought possibly to involve the capsule (Stage C) responded so well to estrogens that it became a Stage A or Stage B as appraised by digital examination. These four patients were operated upon and are included in the series. None of them had recurrence.

In general, the extent of the carcinoma found at operation tended to be greater than expected from preoperative evaluation. In 55 of the 96 patients the neoplasm was staged at least one stage higher by the pathologist than at the time diagnosis was made, indicating perhaps both the insidious nature of this tumor and optimism on the part of the surgeon. All of the recurrences in the series, however, were in cases in which the lesion was Stage C as classified by postoperative specimen examination.

In eight cases no evidence of carcinoma could be found in the surgical specimen, and in none of these cases has evidence of carcinoma developed since. Six of the eight patients previously had had transurethral resection. Both of the other two had only perineal needle biopsy before operation, and both had received estrogen therapy, one of them for one month and the other for five months before the ablative procedure. In both cases squamous metaplasia was noted on examination of the operative specimen.

TABLE 1.—Description of Tumors by Stages (Goodwin¹)

Stage	Description by Stage	Number of Patients	
		Original	Post-operative
O	Occult	16	8
A	Isolated nodule	30	9
B	Local spread, within prostate	46	49
C	Local extension, capsule and/or seminal vesicle	4	30
D	Metastases	0	0

The operations, essentially a standard retropubic prostatosemiovesiculectomy, were done through a mid-line vertical incision. The puboprostatic ligament was carefully ligated before division to reduce venous bleeding. To facilitate approximating the vesical neck and membranous urethra, Vest² sutures were utilized to anchor the bladder down to the perineum. In most patients direct anastomosis was not attempted. The urethral catheter was removed between the seventh to the tenth day and the perineal sutures were cut on the tenth day. The average hospital stay for all patients was 14.7 days.

Orchiectomy was done at the time of operation in 54 cases, and at a later date in four cases. Sometimes orchiectomy was dictated by findings at operation; at other times the philosophy of the individual surgeon determined whether or not orchiectomy should be done. Similarly, estrogen therapy was given postoperatively for varying periods to about half the patients. For these reasons, this report is not strictly speaking a "surgical series"; it is probable the orchiectomy and estrogen therapy extended the lives of patients who had carcinoma left behind after the operation.

Results

Operation was done more than five years ago in 44 cases. Nine of the patients (eight of whom were clinically free of cancer when last seen) have been lost to follow-up. Three have died with cancer, three without. One is alive with known cancer. Thus, of 33 patients who have been followed five years or until cancer was detected, 28 are alive with no evidence of cancer.

In 25 cases more than ten years has passed since operation. Eleven of the patients (ten of whom were clinically free of cancer when last seen) have been lost to follow-up. Three have died of cancer, three without. Thus, of the 12 patients who were followed for ten years or until cancer was detected, eight are alive with no evidence of cancer.

TABLE 2.—*Postoperative Complications in 96 Cases of Total Retropubic Prostatectomy*

<i>Description of Complication</i>	<i>Number</i>
No Complications	60
Vesical Neck Contracture	14
Requiring dilatation	7
Requiring incision or excision	7
With calculus	3
Phlebitis:	8
With pulmonary embolus	3
Without pulmonary embolus	5
Rectal Injury:	4
Primary cloture	2
Secondary cloture	1
Multiple operations to close	1
Post-Operative Oliguria	3
Wound Infection	2
Myocardial Infarction	1
Hepatitis	1
Osteitis Pubis	1
Obturator Paresis, Temporary	1
Post-Operative Hemorrhage, Delayed	1

There were no operative deaths. The shortest period between operation and death was 26 months.

Complications

There was a significant number of complications (Table 2). All patients were sexually impotent after operation. Only 44 of the 96 have achieved perfect urinary control. Another 45, however, have sufficiently good control that they wear no device or protective pads. Five, however, must wear a device of some sort during the day and two patients describe their control as nil.

Excluding incontinence and impotence, 60 patients have been free of complications. Complications in the others are described in Table 2.

In four patients the rectal wall was pierced at the time of dissection of the prostate from the rectum. In two patients injury to the rectal wall was noted at the time of operation and was repaired without colostomy and without postoperative morbidity. In another, the injury was noted on the second postoperative day, whereupon the wound was opened, the urethra and bladder were separated, the rectal wall was closed and the bladder was again brought down to the membranous urethra. Colostomy and cystostomy were done. No further problems occurred and the colostomy was later closed. In the fourth case of rectal injury, the tear was noted at operation and with the assistance of a general surgeon repair was attempted without colostomy, but rectovesical fistula developed and colostomy was then carried out. Two subsequent

attempts by the perineal route were necessary before closure of the fistula was accomplished. This was followed by a perineal incisional hernia which required still another operation for repair. Today the patient is well and without evidence of recurrence.

In three of the four cases of rectal injury, the neoplasm had invaded the capsule. No rectal injuries have occurred in the past three years.

Excess cicatricial tissue formation at the vesical neck, resulting in stricture, was a problem in 14 patients. In one patient suprapubic transvesical excision, and in six a Collings knife transurethral incision were necessary. In the remaining seven, occasional dilatation with urethral sounds has been adequate. In three cases stones formed in the vesical neck or in the membranous urethra and had to be removed cystoscopically. We have been unable to determine why excessive cicatricial tissue develops in some cases and not in others.

The oliguria that developed in three patients was interesting in that it was not accompanied by or preceded by recognized shock, excessive loss of blood dehydration or third compartment formation. It abated spontaneously, beginning on the third postoperative day, with gradual increase in urinary output thereafter. Presumably it was due to edema of the ureteral orifices.

Comment

Until clear-cut evidence is available to indicate conclusively which means of treatment preserves the most useful years of living with the least cost in money and morbidity, choice of treatment for the patient with early carcinoma of the prostate must remain somewhat philosophical. The urologist must decide whether the danger, morbidity, inconvenience and expense of operation are justified by a reasonable increase in the patient's chances of living without prostatic cancer. We believe the results justify further surgical treatment of selected patients with early prostatic carcinoma. The fact that evidence of recurrence was found only when cancer had spread beyond the parenchyma of the prostate before operation justifies the continued use of strict standards of selection of patients.

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Leg Cramps (Systremma) and "Restless Legs" Syndrome

Response to Vitamin E (Tocopherol)

SAMUEL AYRES, JR., M.D., AND RICHARD MIHAN, M.D., *Los Angeles*

■ *A clinical investigation into the therapeutic value of vitamin E (tocopherol) in certain dermatological conditions of obscure etiology led to the incidental observation that this compound produced beneficial effects in some of the patients who were suffering from frequent and severe nocturnal leg cramps. Nearly all of the patients with leg cramps received prompt and gratifying relief from their symptoms while taking vitamin E in the form of d, alpha-tocopheryl acetate, 100 I.U. three times a day before meals. The group included 24 private patients with leg cramps and two with the "restless legs" syndrome, probably a related condition. One of the patients with leg and foot cramps also had severe nocturnal rectal cramps which were also relieved.*

Nocturnal leg cramps constitute a relatively common complaint in the general practice of medicine and may be very distressing to the patient. Not only is the cause obscure and the treatment relatively unsatisfactory, but even its proper medical name, systremma (anything twisted up together), is unknown to most physicians.

THE PRESENT STUDY originated as a by-product of an investigation into the usefulness of vitamin E in the management of several obstinate dermatological conditions, especially pseudoxanthoma elasticum and epidermolysis bullosa.¹

Since the discovery of vitamin E nearly 46 years ago, a large volume of literature on it has accumulated, including hundreds of reports of animal and

laboratory experiments, clinical investigations and at least five international conferences, two of which were sponsored by the New York Academy of Sciences.

Inasmuch as this vitamin plays an essential role in practically all body tissues in protecting vital cell membranes and intracellular structures from damage by lipid peroxidation (antioxidant effect) and possibly also in facilitating activation of certain enzyme systems, a breakdown either in supply, absorption or utilization of vitamin E might be expected to produce a wide spectrum of symptoms and disease processes.^{2,3,4,5,6}

One of the most commonly observed manifestations of a vitamin E-deficient diet in many experi-

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TABLE 1.—*Systremma (Leg Cramps) Treated with Vitamin E (Tocopherol)*

<i>Case</i>	<i>Sex and Age</i>	<i>Duration</i>	<i>Frequency</i>	<i>Severity</i>	<i>Treatment Daily Dose</i>	<i>Results</i>	<i>Comments</i>
1	M 70	1 yr. +	Nightly or oftener	Severe arms & legs	300 IU 2 mo.	Excellent	Only 1 cramp in 2 mo.
2	M 84	10 yr.	Nearly every night	Severe 5-10 min.	300 IU 3 mo.	Moderate	Letter from patient: "Cramps have diminished"
3	F 78	20 yr.	Nightly or sev. \times a night	"Jumpy legs" severe	300 IU 2 mo.	Excellent	"Restless legs" syndrome complete cure; unresponsive to Dilantin® and Benadryl®
4	M 61	1 yr.	Every other night	Severe	300 IU 3½ mo.	Excellent	Complete control. Only partially controlled with quinine.
5	M 77	5 yr.	2 \times a week	Severe 15 min.	300 IU 3½ wk.	Excellent	Complete control
6	F 28	1½ yr.	Every night	Severe at times	300 IU 2 mo.	Excellent	Marked improvement. Quinine, Librium® and muscle relaxant previously ineffective
7	F 60	3 wk.	Every night	Severe	300 IU 2 mo.	Excellent	Complete control
8	M 57	5 yr.	1 or 2 \times a month	Moderate 5 min.	300 IU 2 mo.	Excellent	Complete control
9	M 76	6 yr.	2 or 3 \times a week	Moderate	300 IU 2 mo.	Moderate	Cramps reduced about ¾
10	M 88	2 yr.	Every other night	Severe 10 min.	300 IU 2 mo.	Excellent	Cramps at night and also after walking. Reduced to 2 or 3 times a month.
11	F 32	Sev. yr.	2 \times mo.	Severe 15 min.	300 IU 4½ mo.	Excellent	Complete control
12	F 49	5 yr.	3 \times wk.	Severe	300 IU/1 mo. 100 IU/1 mo.	Excellent	Only 1 cramp in 2 mo.
13	M 75	3 yr.	Every other mo.	Severe 15-20 min.	200 IU 1½ yr.	Excellent	Complete control
14	F 74	3 yr.	3-4 \times wk., sev. \times a night	Severe 15 min.	200 IU 1½ yr.	Excellent	99% control
15	M 60	15 yr.	2 \times mo.	Severe 10-15 min.	300 IU 3 mo.	Excellent	Complete control
16	F 70	5 yr.	1 or 2 \times mo.	Moderate	300 IU 5 mo.	Excellent	Cramps in feet. Complete control.
17	F 80	Sev. yr.	Nightly	Severe	300 IU 3 mo.	Excellent	Only 3 minor cramps in 3 mo. Quinine ineffective.
18	F 25	Sev. yr.	1 \times wk.	Mild	300 IU 2 mo.	Excellent	Complete control
19	F 68	3 yr.	2 or 3 \times a wk.	Severe	300 IU 6 wk.	Excellent	Had severe nocturnal rectal cramps, as well as foot cramps. Both controlled.
20	F 58	Many yr.	2 \times mo.	Mild	300 IU 7 mo.	Moderate	Only 2 mild cramps in 3 mo.
21	F 60	3 yr.	3 \times mo.	Moderate	300 IU 9 mo.	Excellent	Only 2 or 3 minor cramps in 9 mo.
22	F 68	3 yr.	2 \times wk.	Moderate	300 IU 2 mo.	Moderate	Only occasional cramp after unusual exercise.

(Table 1 is continued on next page)

Continuation of Table 1.—*Systemma (Leg Cramps) Treated with Vitamin E (Tocopherol)*

Case	Sex and Age	Duration	Frequency	Severity	Treatment Daily Dose	Results	Comments
23	F 61	10 yr.	Nightly	Severe 5 min. +	300 IU 5 wk.	Excellent	After 5 wk. only 1 or 2 × a wk. Very mild.
24	F 26	2 yr.	2 or 3 × nightly	Severe	300 IU 4 wk.	Excellent	No cramps after 2 wk.
25	F 37	10 yr.	Nightly	"Restless legs" severe	300 IU/6 wk. 200 IU/4 wk.	Excellent	Complete relief
26	F 78	Sev. yr.	Nightly	Severe ½ hr.	300 IU/3 da. 100 IU/6 wk.	Excellent	Almost complete relief

mental animals, including the rhesus monkey, is an acute and extensive degenerative change in skeletal muscles and, in some instances, in cardiac muscle.⁷

Early in our dermatological study several patients mentioned that they had suffered from severe nocturnal leg cramps but that after they began taking vitamin E their leg cramps had ceased. The experimentally induced muscle damage resulting from a vitamin E-deficient diet suggested the possibility that nocturnal leg cramps might be caused by either a mild deficiency or faulty utilization of this vitamin in the leg muscles.

Encouraged by these results, we began to question all the patients in our study, as well as all new patients, regardless of their skin problems, concerning a history of leg cramps. As a result, a total of 24 patients with leg cramps and two with "restless legs" syndrome were given d, alpha-tocopheryl acetate, 100 I.U. three times a day before meals.* Nineteen of these 26 patients had symptoms classified as severe, five as moderate and two as mild. Excellent results (90 to 100 percent relief) were obtained in 22 patients and moderate improvement in four. Relief was prompt, usually occurring within the first week or two, suggesting therapeutic specificity. No other drugs were given. Two patients who had obtained almost complete relief discontinued the vitamin after about two months. There was a gradual return of symptoms within four or five weeks in both patients, but the cramps disappeared again on resumption of medication. It probably would be possible to reduce the dose to 200 or 100 I.U. per day after the condition has been brought under control.

*It is important in prescribing the vitamin that it be taken at least 10 or 15 minutes before mealtime and that it not be administered simultaneously with medication containing iron, and mineral oil should also be avoided, since iron and mineral oil tend to lessen the absorption of vitamin E.

The brand which the authors have used most often is manufactured by Professional Drug Products, Los Angeles, California, and is distributed by Horton & Converse, 2005 Wilshire Blvd., Los Angeles, Ca. 90057. U.S.V. Pharmaceutical Corporation (formerly U.S. Vitamin Corp.) also produces a brand called Aquasol® E, which is a water-solubilized form useful for persons who are unable to tolerate or absorb fats, since vitamin E is normally a fat-soluble vitamin.

One of these patients, a 78-year-old woman, instead of having actual cramps complained of "restless legs," or as she expressed it, "jumpy legs," which had bothered her severely for 20 years, interfering with sleep nightly and only partially relieved by Dilantin® and Benadryl®. She received complete relief with the vitamin E. Another patient, a 37-year-old woman who nightly for ten years had been troubled with "restless legs" to the point of interference with sleep, obtained complete relief after two weeks of vitamin E therapy, and the improvement has been maintained on 200 I.U. daily. One patient in this series, a 68-year-old woman, in addition to having frequent leg and foot cramps also had severe nocturnal rectal cramps, necessitating the application of heat. Both manifestations responded to vitamin E (See Table 1).

Discussion

A review of the literature on leg cramps failed to disclose any scientific name for this entity. Mrs. Helen Tibbs, of the Los Angeles County Medical Library staff, after consulting various cross-references, came to our rescue with a copy of Dorland's Medical Dictionary, 20th Edition, where "systemma" was defined as "cramps in the calf of the legs," from the Greek, meaning "anything twisted up together." We herewith submit "systemma" as a proper term not only for leg cramps but for cramps involving other muscle groups as well.

Most current texts on internal medicine and orthopedic surgery give scant attention to nocturnal leg cramps, despite the fact that it is recognized as a fairly common complaint. According to Perchuk,⁸ "Nocturnal leg cramps are symptomatic of an abnormal muscle metabolism and are present in a variety of conditions. Although the calf is generally involved, other muscle groups may be affected, and as illustrated in one case history, even the upper extremity may be the site of nocturnal cramps." Perchuk and coworkers⁹ obtained grati-

fyng relief by oral administration of a muscle relaxant, methocarbamol (Robaxin®) in which "therapy was based on the drug's ability to suppress reflex skeletal muscle spasm at the level of the spinal cord. Thus, proprioceptive stimuli arising out of ischemic conditions, imbalances in metabolism or calcium-phosphorus imbalance are blocked before they are able to trigger clonic or tonic contractions."

Perhaps vitamin E may correct the metabolic defect at its source without the necessity of any blocking action. Any medication which is able to restore normal function with no risk of serious side-effects would appear to be suitable.

Leg cramp is a frequent complication of pregnancy, according to Salvatore,¹⁰ who reported an incidence of 33 percent in a series of 980 pregnant women. In 6.1 percent the cramps were severe enough to require treatment.

There have been a number of papers on "restless legs," beginning with Allison's¹¹ and including papers by Tatlow,¹² Masland,¹³ Ekblom,¹⁴ De Jong,¹⁵ Gorman, et al,¹⁶ and Roberts.¹⁷ While leg cramps and "restless legs" are usually dealt with as separate entities, certain features, especially the site, the muscles involved and response to treatment, suggest a close relationship. Etiologic explanations and therapeutic achievements in both conditions have left much to be desired.

Roberts,¹⁷ in a comprehensive paper based upon clinical and laboratory investigations of 131 patients affected with spontaneous leg cramps (SLC) and restless legs (RL), offers convincing evidence that these manifestations, frequently occurring in the same patient, are part of the same process and are caused by extremely low blood sugar levels due to diabetogenic hyperinsulinism (DH), which he considers to be a precursor to true diabetes.

Returning to our own modest series of 26 cases of leg cramps (systemma) and "restless legs," no laboratory studies of any kind were carried out, and the cases are presented merely as an interesting clinical observation. In view of the brilliant results obtained with a simple therapeutic agent without any drugs to block nerve impulses or dietary management, one cannot but speculate on exactly what the mode of action of vitamin E may be in relieving leg cramps. At least two contributions^{18,19} indicate that tocopherol improves glycogen storage in the muscles.

Tocopherol is a fat-soluble vitamin composed of a number of fractions. Many investigators have

shown that for all practical purposes the alpha fraction is so much more physiologically active than all the other fractions, the latter can be ignored and deficiency states produced by vitamin E-deficient diets can be corrected by giving alpha-tocopherol alone. The use of mixed tocopherols merely dilutes the effectiveness of the preparation.

Again, the acetylated form protects the vitamin from premature oxidation before being absorbed through the intestinal wall. Vitamin E is absorbed much more effectively if it is taken on an empty stomach, at least 10 or 15 minutes before meals. The natural vitamin is more potent than the synthetic. The designation d, alpha-tocopheryl acetate specifies the acetylated form of the natural alpha fraction of tocopherol. An average adult dose is 100 I.U. (not mg) three times a day before meals. For persons unable to absorb fats, a water-solubilized form, Aquasol E, is available. Diets high in polyunsaturated fats increase the requirements for vitamin E, as does the simultaneous administration of iron. The frequent use of laxatives, especially mineral oil, interferes with the absorption of vitamin E.

Serious side-effects are virtually nil. Because of the observed tendency of vitamin E to improve glycogen storage in the muscles, diabetic persons who are taking insulin should probably be started on smaller doses, which can be gradually increased as the insulin dosage is adjusted. Patients with severe hypertensive heart disease should also be started on smaller doses, although the hypertension may later be benefited.

Quinine, which is usually prescribed for this condition, is only partially effective and always carries the possibility of unpleasant side-effects. Tocopherol plays an important role in intracellular enzyme and antioxidant processes of various tissues, and an adequate supply appears to be essential for the physiological functioning of muscle tissues. The fact that the leg muscles are undergoing cramps or spasms even while at rest suggests a lack of some essential factor, and the prompt relief afforded by tocopherol may indicate an inadequate supply, inadequate absorption or defective utilization of this vitamin.

Although placebo studies would have made the results here reported more impressive, they were not carried out because none of the patients consulted us for the leg cramps, and the observations reported in this study were coincidental to an investigation into the value of tocopherol in certain

dermatological conditions. For these reasons no detailed medical studies pertaining to the circulatory system or blood chemistry were done. Even so, it was felt that a brief clinical report might be of assistance to others wishing to carry out more detailed investigations into this common and painful disorder for which no really effective treatment is at present available.

TRADE AND GENERIC NAMES OF DRUGS

<i>Aquasol</i> ® E d, alpha-tocopheryl acetate (aqueous vitamin E)
<i>Benadryl</i> ® diphenhydramine hydrochloride
<i>Dilantin</i> ® diphenylhydantoin
<i>Librium</i> ® chlordiazepoxide hydrochloride

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TRICKS IN TUBAL INSUFFLATION

"One of the little tricks in tubal insufflation is to insert the uterine cannula, holding it with the left hand, and press the uterus down against the cannula—thus occluding the cervix without the use of a tenaculum. The interesting thing that happens is that as the gas passes through the tubes and bubbles up against the peritoneal surface on the top, one can feel a little sense of crepitation. This is very comforting because sometimes you hear gas and sometimes you don't; sometimes it's on one side, sometimes on the other. But this crepitation almost assures you that gas has passed through.

"Incidentally, in doing tubal insufflations, one is wise to flush out the long tube from the instrument to the cannula with carbon dioxide before starting the test. If you don't, then what you are really insufflating with is common air because that's what goes in and probably goes through the tubes long before the carbon dioxide from the machine even reaches the cannula. If you use air, then the patient has much more prolonged shoulder pain than if you use gas."

—PENDLETON TOMPKINS, M.D., San Francisco
Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 15, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

CASE REPORTS

Chiari-Frommel Syndrome As A Part of the Zollinger- Ellison Multiple Endocrine Adenomatosis Complex

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ZOLLINGER AND ELLISON¹ described in 1955 a syndrome in which recurrent peptic ulceration and gastric hypersecretion are associated with nonbeta cell tumors of the pancreas. Because many patients with the Zollinger-Ellison syndrome have neoplastic changes in other endocrine glands, the entity is now considered to be a variant of the multiple endocrine adenomatosis (MEA) syndrome.^{2,3} The MEA syndrome is characterized by hyperplastic, adenomatous, or carcinomatous changes in multiple endocrine organs, most frequently the pituitary, parathyroids and pancreatic islets²; the thyroid and adrenal glands are involved less often. It was recognized in 1954 that the MEA syndrome represents a familial disorder transmitted by an autosomal dominant gene⁴; subsequent reports have supported this observation.⁵⁻⁷ In this paper we report upon a patient who appeared to have the Zollinger-Ellison syndrome, but was later considered to have an unusual pituitary variant of familial multiple endocrine adenomatosis.

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Report of a Case

A 23-year-old housewife had been in good health until after her first pregnancy, which was normal. Following parturition, she felt well, but did not menstruate for several months, and galactorrhea persisted although she made no effort to nurse her infant. Administration of contraceptive tablets, begun six months postpartum, resulted after three months in cyclic menses and cessation of galactorrhea. She then discontinued the tablets. Amenorrhea and galactorrhea recurred, and persisted for two years, when dilatation and curettage demonstrated "atrophic endometrium." Following this procedure, the cyclic administration of ethynodiol diacetate with mestronol (Ovulen®), 1 mg daily, suppressed lactation and induced regular menstrual flow. The patient again discontinued the agent, and amenorrhea and galactorrhea promptly recurred.

A half year after delivery of her child, the patient had experienced persistent postprandial epigastric pain and burning, unrelieved by antacids. Roentgen study of the upper gastrointestinal tract demonstrated an ulcer in the duodenal bulb. For three years, while taking a bland diet, antacids and atropine, she felt well except for an occasional exacerbation of the ulcer symptoms. When she was 26 years of age epigastric pain recurred, accompanied by bleeding from the upper gastrointestinal tract, sufficiently severe to necessitate blood transfusions. She then remained free of ulcer symptoms for one year, when acute perforation of the duodenal ulcer with secondary peritonitis occurred. The perforation was closed surgically. Because the symptoms persisted over the next four months, vagotomy and pyloroplasty were performed electively. During this procedure a 2.5-cm, well encapsulated, spherical mass was found attached to the lower surface of the gallbladder and the upper surface of the cystic duct. The gallbladder and tumor were excised. The pathologic diagnosis was "islet cell adenoma."

The patient was virtually asymptomatic during the ensuing 15 months. Severe epigastric and back pain then recurred, and radiologic studies demon-



Figure 1.—Chronic deformity of the duodenal bulb is demonstrated, with loss of mucosal folds in the second and third portion of the duodenum. There is severe excessive intraluminal secretion throughout the small intestine. The small bowel is moderately dilated, and decidedly edematous.

strated a large ulcer crater in the duodenal bulb. After three weeks of intensive medical management in hospital, the symptoms had improved only minimally and the patient was transferred to the University of California Medical Center, San Francisco. She was then (March 1967) 29 years old.

On admission she described minimal discomfort as long as continuous antacid therapy was maintained. There had been no recent hematemesis, melena or hematochezia. She denied diarrhea; her stools were formed, with one to three movements daily. She had gained five pounds in the month before admission. She was taking ethynodiol diacetate with mestronol, 1 mg daily cyclically; propantheline, chlorthalidone, and antacids.

Family history was significant. Her father had undergone partial gastrectomy for intractable peptic ulcer disease at the age of 45 years; he has since been asymptomatic. Her 37-year-old brother had recurrent renal stones and was found to have hyperparathyroidism; he had not yet been treated surgically. A 27-year-old brother had recurrent hypoglycemic episodes because of a malignant insulin-secreting tumor of the pancreas.

When examined on admission the patient was alert, moderately obese, and in no distress. Blood pressure was 130/80 mm of mercury and the pulse rate 84 per minute. She was afebrile. Her skin was warm and moist, with healed acneiform lesions on face and chest. There was no abnormal coloration or fine wrinkling around the eyes and mouth. Although scalp hair was thin, axillary and pubic hair was normal. Eyes (including visual fields) were normal. The neck was normal. The breasts were symmetrical and without masses; milk could be expressed from the right nipple. A soft systolic ejection murmur, heard at the base of the heart, radiated to the carotid vessels. The liver edge was felt at the right costal margin. Other findings, including those on neurologic examination, were unremarkable.

Pertinent laboratory data included hemoglobin 9.2 grams per 100 ml, packed red blood cell volume 35 ml per 100 ml; white blood cell count 8,200 per cu mm; serum amylase 120 Somogyi units per ml (normal, 70-150 units); serum lipase 0.8 units per ml (normal 0-1.5 units); serum alkaline phosphatase 5 Shinowara, Jones and Reinhart

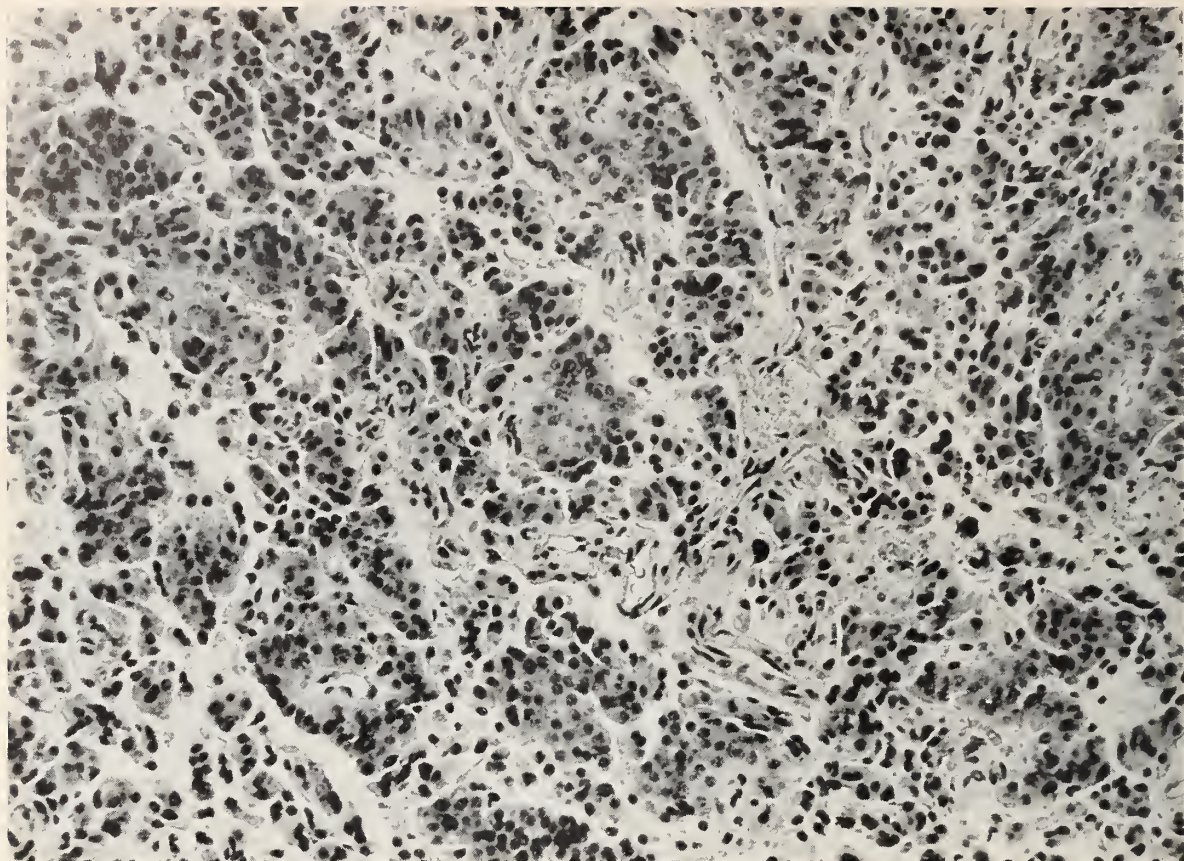


Figure 2.—Pancreas, showing multiple irregularly shaped islands of cells, rare mitotic figures, and no definite pleomorphism. No normal pancreatic tissue is seen. (Hematoxylin and eosin, $\times 150$.)

units per 100 ml (normal 2-10 units); total bilirubin 0.3 mg per 100 ml; bromsulphalein retention 2.6 percent in 45 minutes. Serum calcium ranged, on several determinations, from 9.9 to 11.7 mg per 100 ml (normal, 8.8-10.4 mg); serum phosphorus 2.4-3.3 mg per 100 ml (normal, 3.0-4.5 mg).

Tubular reabsorption of phosphorus on a low phosphate intake (by using aluminum hydroxide gel as an antacid) was 48 percent. Plasma 17-hydroxycortisol at 8 a.m. was 22.7 mcg per 100 ml (normal, 5-20 mcg); urinary 17-hydroxycorticoid excretion, 9.5 mg F per 24 hours (normal, 4-10 mg); urinary 17-ketosteroid excretion, 10.2 mg DEA per 24 hours (normal, 5-15 mg). Twenty-four hour urinary pituitary gonadotrophin was less than 5 mouse units and negative at 5, 40, and 80 mouse units. Serum protein-bound iodine was 8.8 mcg per 100 ml; red blood cell triiodothyronine uptake, 10 percent (normal 10-20 percent). The patient was not taking exogenous estrogen.

The glucose tolerance test gave the following values: fasting, 84 mg per 100 ml; 30 minutes, 122; 1 hour, 135; 2 hours, 112; 3 hours, 110; 4

hours, 60; and 5 hours, 71 mg per 100 ml. Growth hormone determinations (normal, 0 to about 10 m μ g per ml), performed simultaneously with the glucose evaluations, yielded levels of: fasting, 3.9 m μ g per ml; 1 hour, 0.5 m μ g. After infusion of 30 grams of arginine, growth hormone values were: fasting 0.6 m μ g per ml; at 30 minutes, 3.0; 60 minutes, 6.5; 90 minutes, 3.9; and 120 minutes, 0.9 m μ g per ml.

Twelve-hour overnight gastric secretion total volume was 1,250 ml; free acid, 84 mEq, total acid 99 mEq. Basal and augmented gastric secretion determinations were not completed because of poor patient cooperation.

Normal laboratory values included VDRL, serum electrolytes, uric acid, blood urea nitrogen, serum cholesterol level, total serum protein, and serum electrophoresis. Radiologic examination of chest, hands, and skull showed no abnormality.

Upper gastrointestinal x-ray study demonstrated active duodenal ulceration with deformity of the duodenal bulb; the remainder of the duodenum and small bowel were dilated and decidedly edema-

tous with an excess of intraluminal fluid (Figure 1).

These findings were compatible with the Zollinger-Ellison syndrome.

One month after admission, total gastrectomy was performed. At laparotomy, multiple tumor masses were found in the pancreas and in periaortic nodes. Biopsy of one of these masses showed well-differentiated islet cell carcinoma (Figure 2). The patient has remained free of ulcer symptoms during the ensuing year. Serum calcium values have on occasion been found to be elevated (11.7 mg per 100 ml), with phosphorus level of 3.1 mg per 100 ml; as yet she has had no other manifestations of hyperparathyroidism. She is being closely followed in the endocrine clinic.

Discussion

The presence of an islet cell carcinoma, gastric hypersecretion, and fulminant ulcer diathesis establishes the diagnosis of Zollinger-Ellison syndrome in this patient. Familial multiple endocrine adenomatosis is suggested by the pancreatic tumor and probable early hyperparathyroidism, and by hyperparathyroidism in one sibling and an insulin-secreting islet cell carcinoma of the pancreas in another. The unusual aspect of her illness is the persistence of postpartum amenorrhea and galactorrhea as the pituitary manifestation of MEA.

Postpartum amenorrhea and galactorrhea in association with utero-ovarian atrophy, when unaccompanied by intracranial tumor, are the Chiari-Frommel syndrome⁸; amenorrhea and galactorrhea accompanied by a pituitary tumor, with or without pregnancy, are known as the Forbes-Albright syndrome.^{9,10} Amenorrhea has been previously reported in patients with MEA,^{5,11} but not in association with prolonged galactorrhea, the amenorrhea being secondary usually to a space-occupying hypophyseal tumor. The well-known association of galactorrhea with acromegaly in patients with pituitary tumor¹² must be considered when lactation develops in persons with MEA.

The patient described here showed no physical evidence of a pituitary tumor: the sella turcica was not enlarged, there was no apparent acromegaly, and the visual fields were normal. Immunochemical assay of growth hormone levels during the glucose tolerance test and arginine infusion showed them to be normal; and pituitary gonadotrophins in the urine were absent, a characteristic finding in Chiari-Frommel syndrome.

The Chiari-Frommel syndrome is believed to be due to pituitary dysfunction, of a type not understood. One hypothesis is that there is failure of pituitary gonadotrophin secretion, resulting in decreased estrogenic activity with concomitant utero-ovarian atrophy and amenorrhea. The postpartum secretion of milk is considered to be controlled by the secretion of prolactin by the pituitary gland. Prolactin secretion is under chronic direct or indirect inhibition by the central nervous system; if such inhibition is removed, prolactin secretion is enhanced.¹³ Recent reports indicate that these neurogenic and humoral factors act through the hypothalamus, causing a decrease in the secretion of a neurohormonal factor, "prolactin inhibiting factor" (PIF).^{14,15} Ischemia of the hypothalamo-hypophyseal tracts during parturition might explain prolactin excess, if the area of damage could effectively block hypothalamic influence on anterior pituitary function. Serum prolactin levels have been found elevated in some patients with Chiari-Frommel syndrome.^{16,17} A second hypothesis offered in explanation of this syndrome is that hyperfunction of eosinophilic cells in the anterior pituitary leads to excess prolactin secretion.¹⁸

The patient in the present case was not in clinically apparent shock during delivery of her child, and there is no physical evidence of a space-occupying hypophyseal tumor. A prolactin-secreting adenoma, or a small tumor that is blocking hypothalamo-hypophyseal pathways could explain her symptom complex; but at present there is no evidence for such a neoplasm. This is especially pertinent in view of a recent report by Young and coworkers¹⁹ of two patients in whom supposedly benign Chiari-Frommel syndrome evolved to the Forbes-Albright syndrome associated with hyperadrenocorticism. The patient in the present case will be followed closely for the possible later appearance of a pituitary tumor.

As far as we are aware, this is the first report of the Chiari-Frommel syndrome associated with the Zollinger-Ellison multiple endocrine adenomatosis complex. At present the patient shows no other evidence of pituitary hyperfunction or tumor.

Summary

Persistent postpartum amenorrhea and galactorrhea without pituitary tumor (Chiari-Frommel syndrome) were the unusual pituitary manifestations of multiple endocrine adenomatosis in a 23-year-old woman who had been well until delivery

of her first child. Six months postpartum, duodenal ulcer disease with gastric hypersecretion became evident, and was fulminant over the next several years.

Islet cell carcinoma of the pancreas with metastasis to periaortic nodes was found at age 29, establishing the diagnosis of Zollinger-Ellison syndrome. There was persistent hypercalcemia. Probable hyperparathyroidism in the patient, and a family history of hyperparathyroidism and insulin-secreting islet cell carcinoma of the pancreas supported the diagnosis of familial multiple endocrine adenomatosis.

Following total gastrectomy the patient remained free of ulcer symptoms for a year up to the time of this report.

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Sublingual Dermoid Tumors

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A YOUNG GIRL was seen with a mass bulging up into the floor of her mouth. It had been slowly growing and lately seemed to have impeded her speech. Examination revealed the tumor to be of dough-like consistency that retained pitting after pressure on it. The diagnosis almost had to be dermoid cyst. The purpose of this paper is to renew interest in this infrequent¹ but interesting and unforgettable tumor.

Of all the dermoid cysts found in the body, 6 percent are located in the head and neck and 1.38 percent involve the floor of the mouth and tongue.² The cysts may vary in size from 4 cm to 10 cm or more in diameter and the incidence is about equally divided between the sexes (males 51 percent, females 49 percent). Most of the patients (60 percent) are under 35 years of age.

It is accepted that dermoid cysts derive from ectodermal differentiation of multipotential cells that were probably pinched off at the time of closure of the anterior neuropore. Erich³ differentiated inclusion dermoid cysts from the congenital dermoid cysts of teratoma type which arise from embryonic germinal epithelium. The true inclusion dermoid developing along embryonic clefts and lines of fusion is lined with stratified epithelium which possesses sebaceous and sweat glands and hair follicles. Practically all inclusion dermoid cysts are found about the head and neck.⁴ The mylohyoid muscle separates dermoid cysts of the floor of the mouth from those occurring in the submental and submaxillary areas.⁵ When cysts become very large, even though in the floor of the mouth, they may bulge into the submental area. Clinically they may be divided into three groups, though blending is possible: (1) The sublingual

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or genioglossal tumors present as masses under the tongue, and as they grow they push the tongue backward. (2) The geniohyoid group is made up of painless swellings in the submental area, which can give the appearance of a "double chin." (3) The lateral series appear under the mandible in the submaxillary area. As they expand, they may grow downward and toward the hyoid bone or press up into the floor of the mouth, pushing the tongue toward the opposite side. Pain is very unusual in any of the three types. Conditions that must be considered in differential diagnosis are ranula, cystic hygroma, branchial cleft cysts, lipomas, thyroglossal duct cysts, and tumors or inflammations of the submaxillary glands. The treatment is surgical.^{6,7}

The following five cases are illustrative:

Case 1. A 7-year-old Negro girl had a slowly enlarging submental mass for nearly a year. On examination of the patient's neck a cystic-like submental mass about 2x2 inches was noted. It rose into the anterior floor of the mouth, pushing back the tongue and also giving the child the appearance of having a double chin. She had some difficulty in talking.

Submental triangle dissection was performed. The tumor mass was deep to the mylohyoid muscle and was dissected from the pharyngeal mucosa. It was 3 to 4 cm in diameter, and the diagnosis was dermoid cyst. The incision healed nicely and much of the difficulty in talking subsided.

Case 2. A 27-year-old Negro man was seen because of a right submaxillary mass that had been enlarging for many months. Right submaxillary triangle dissection was performed and a 10 cm x 4 cm cystic-like doughy mass was removed from above the mylohyoid muscle. The mass pushed up into the floor of the mouth, deforming the pharynx and tongue. The diagnosis was dermoid cyst. After recovery from the operation the patient was able to eat and talk better.

Case 3. An 8-month-old Negro girl had been observed periodically since birth because of a large cystic mass in the anterior floor of her mouth. About 3 cm in diameter, the tumor pushed her tongue straight back.

Shortly after birth an incision and drainage had been performed and a dark, thick, odorous substance removed. The mass enlarged again in two weeks, and incision and draining was done again. A culture of the material, sterile at the time of the

first procedure, now grew hemolytic staphylococcus. Antibiotics were administered.

The baby was put into hospital and a seton was inserted through the cystic mass after it was thoroughly irrigated. Total excision was not performed because of severe inflammation.

At eight months of age, the cystic-like mass had again increased to a large size and complete surgical excision was urged. Under general anesthesia, the tumor mass was totally removed by intraoral dissection. The pathological diagnosis was dermoid cyst. There was no postoperative complication.

Case 4. A 23-year-old Caucasian man had noticed an enlarging mass in the right submaxillary area for one to two months. On examination a huge cystic-like mass was seen in the right submaxillary area and floor of the mouth. The patient's tongue deviated to the right. On palpation, pitting of the mass and a doughy consistency were noted. Right suprahyoid neck dissection was performed and a mass more than 9 cm in diameter was removed. The diagnosis was dermoid cyst. Two months later the patient's tongue was normal and he had no difficulties.

Case 5. The patient, a 10-year-old Caucasian girl had had a mass in the left submaxillary area for over a year, and it was slowly enlarging. Examination revealed a 3.5 x 3 cm cyst-like mass with doughy pitting consistency in the left submaxillary area, pushing up into the floor of the mouth.

Left submaxillary dissection was performed and the tumor was found to be deep in the mylohyoid muscle and pushing up into the floor of the mouth. The tumor was removed along with the submaxillary gland. The diagnosis was dermoid cyst.

Discussion

On microscopic examination of sections, all the cysts in the cases here reported were lined with stratified squamous epithelium, with some sebaceous and serous glands seen. Three of the tumors were of the lateral group, appearing under the mandible in the submaxillary area, and one was geniohyoid and one genioglossal.

Surgically it is technically far easier and safer to proceed via the neck to remove these tumor masses, some quite huge, than through the mouth. By this route the lingual and hypoglossal nerves are dissected and preserved and adequate hemostasis is obtained. The mouth is never entered and a clean operative field is left to heal rapidly.

The doughy-like consistency and the pitting on pressure that are characteristic of sublingual dermoid tumor are duplicated in no other tumor in this area. Although a differential diagnosis is necessary, once one palpates this particular kind of tumor he is not likely to confuse it with anything else.

Summary

An infrequent tumor of the floor of the mouth is a sublingual dermoid tumor. It is a large dough-like compressible mass which may elevate the tongue and make talking and swallowing difficult.

It occurs equally in both sexes and is nearly always seen below the age of 35. It is treated sur-

gically and an external approach usually is most satisfactory.

A differential diagnosis between a ranula, cystic hygroma, lipomas and tumor of the submaxillary gland can usually be made just by palpation.

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TEMPERATURE AS A SIGN OF ENDOMETRIOSIS

"In a long conversation with Doctor Alan Grant of Australia, I learned something which, I think, will be of value to all of us. Doctor Grant says that whereas body temperature ordinarily drops sharply the day a menstrual period starts, in patients with early endometriosis there is a sustained rise for a few more days and then it drops down. This seems so logical because these patients have pain—they doubtless have peritoneal irritation. I have started a study of my own patients, the first group being those with proved endometriosis—that is, proved by laparotomy. Of that group, 75 percent had a sustained rise in temperature during menstruation. The second group were those who were suspected of having endometriosis because of nodules in the cul-de-sac, but in whom disease had not been proved by visual examination. Of these, some 60 percent had a sustained rise in temperature during menstrual flow."

—PENDLETON TOMPKINS, M.D., San Francisco
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Cell and Tissue Damage Through Antigen-Antibody Complexes

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THE CONCEPT THAT immunologic injury to specific organs or tissues might occur as a result of antigen-antibody reactions immunologically unrelated to the structures injured was first voiced by von Pirquet¹ almost 60 years ago. In the course of studying serum sickness in humans, he postulated that the coexistence of foreign serum antigens and homologous antibodies in the circulation resulted in the formation of toxic compounds which were probably the cause of the rather specific vascular, renal, cardiac, cutaneous and joint lesions developing in tissues without immunologic relationship to the injected antigen. Support for or proof of this idea was not forthcoming for almost 50 years, during which time it was eclipsed in immunologic dogma by the more direct and easily understood specific antitissue antibody mechanism of immunologic injury. This process depends upon the formation of antibodies capable of reacting with specific antigens of the hosts tissues (autoantibodies) and thereby inducing injury. While this mechanism has been enthusiastically proposed for virtually all diseases of presumed immunologic origin and a host of autoreactive antibodies have been described, it has not been possible to demonstrate a pathogenic role for such antibodies in more than a few instances.

In the past decade, following the lack of general applicability of the antitissue antibody idea, much information has accumulated establishing the role of antigen-antibody complexes *per se* as pathogenetic agents capable of inducing a variety of

injuries, ranging from acute through chronic inflammation to hyaline degeneration in particular anatomic sites. Apparently, the interaction of antigen with antibody forms a macromolecular complex which, if soluble, can circulate in the host and, upon further reaction with serum factors or cells, can injure any tissue in which it fortuitously or by design is deposited.

Experimental demonstration of the pathogenic qualities of antigen-antibody complexes began with the studies of Friedman² and Frieberger³ of the anaphylactogenic properties of mixtures of immune serum and antigen. Later, it was established that the lesions of serum sickness developed at the time of antigen-antibody interaction in the circulation.^{4,5} About ten years ago, independent and quite different lines of investigation in several laboratories all pointed to the actual antigen-antibody complex as a pathogenic agent. The earlier studies of anaphylaxis were extended to demonstrate that purified, soluble antigen-antibody complexes could, by themselves, induce systemic anaphylaxis.⁶ The study of experimental serum sickness employing isotopically labeled antigens and the fluorescent antibody technique made it possible to demonstrate soluble, circulating antigen-antibody complexes during the development of the disease,⁷ and further to demonstrate localization of antigen, host gamma globulin and host complement, presumably as immunologic complexes, in the lesions simultaneously with their development.^{8,9} It was shown that soluble antigen-antibody complexes would induce smooth muscle contraction *in vitro*,^{10,11} produce cutaneous reactions of increased vascular permeability,¹² and even actual vascular necrosis.¹³

Following these observations, a partial definition of those properties of complexes responsible for their pathogenicity has been achieved. Germuth

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and McKinnon⁶ showed that complexes formed in moderate antigen excess, that is, complexes which were small enough to be soluble and therefore able to circulate, and also large enough to be capable of reacting with complement, were most active in producing systemic anaphylaxis. A series of studies by Ishizaka and associates demonstrated some of the molecular characteristics of pathogenic complexes.^{14,15} Using increased vascular permeability in local cutaneous reaction as a test system, they found that (1) all active complexes had two characteristics: they were formed from antibody having an affinity, and they were able to interact with complement; (2) the activity of a complex depended upon the properties of the antibody, not the antigen—rabbit, human and guinea pig antibody formed active complexes, whereas bovine, chicken and horse antibody complexes were inactive; (3) the abilities of complexes to fix to tissues and to react with complement resided in the Fc portion of the antibody molecule—a portion devoid of antibody-combining sites but rich in carbohydrate, and (4) the activity of soluble complexes was associated with a change in the property of optic rotation of the complex. These findings led to the proposal that the configuration of antibody molecules was altered when brought into close apposition in an immunologic complex, and that this altered configuration was responsible for the complexes' changed optic rotation and their ability to fix complement and induce a phlogogenic stimulus.

If all that was needed to produce biologically active complexes was to bring antibody molecules into close apposition and thereby alter their configuration, means other than antigen-antibody reactions to cause apposition of antibody molecules should have a similar effect. It was demonstrated that human gamma globulin and rabbit gamma globulin aggregated by chemical means or by heat developed the ability to fix complement.¹⁶ Some of these aggregates also had an affinity for tissues, and these showed pathologic activity—that is, they increased vascular permeability in cutaneous reactions. In the fixation of complement and induction of skin reactions, these heat and chemically aggregated gamma globulins were qualitatively and quantitatively quite similar to the immunologic complexes. This supported the suggestion that the biologic activity of the antigen-antibody complex was related to the interactions of adjacent gamma globulin molecules with resultant alterations caus-

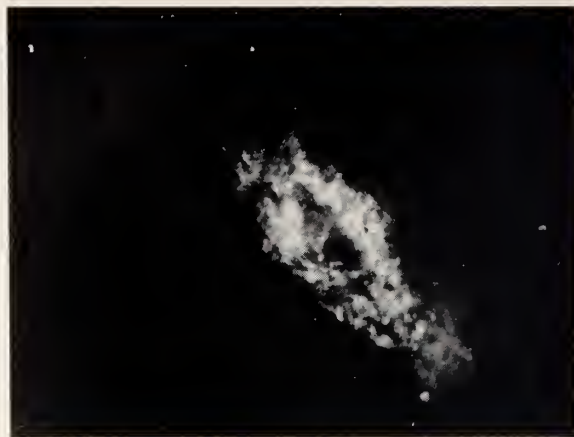


Figure 1.—Fluorescent photomicrograph of a vessel from an Arthus reaction similar to that shown in Figure 2. Section treated with fluorescent antiovine serum albumin to demonstrate the presence of antigen in the vessel wall. Fluorescent stains for antibody and host complement yielded similar fluorescence. $\times 300$.

ing a phlogogenic stimulus. The fact that gamma globulins aggregated nonimmunologically *in vitro* can have biologic activity suggests the possibility that aggregation on a nonimmunologic basis might occur *in vivo*, perhaps among partially denatured or in other ways altered gamma globulins, with formation of pathogenic complexes. If this proves to be so, the concept of gamma globulin complex-induced disease could indeed involve much more than immunologic diseases.

The nature of the disease caused by soluble antigen-antibody complexes is determined by the distribution and extent of their localization in tissues. Thus, the size of the complexes, their concentration, and the duration of their presence in the circulation are of greatest importance. Since these complexes appear to localize in tissues for anatomic and physiologic reasons and not as a result of immunologic specificity, their physical properties are the determining factors. Small complexes ($Ag_2 Ab$) may remain in the circulation for long periods without depositing in tissues and producing injury, while larger complexes seem to be trapped in structures which ordinarily exclude or are permeable to serum proteins. Large concentrations of pathogenic complexes in the circulation for brief periods as seen in conventional serum sickness usually cause exudative polymorphonuclear leukocytic and proliferative endothelial lesions with necrosis of tissue, while lower levels of similar complexes in the circulation for periods of weeks or months cause chronic lesions with hyalin degeneration of vessel walls.¹⁷ Once deposited in the

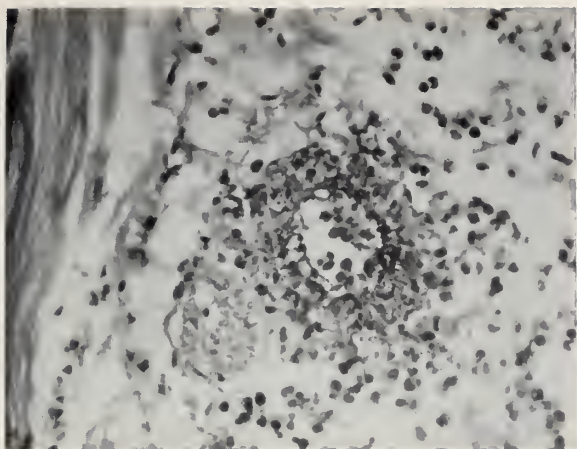


Figure 2.—Photomicrograph of a vessel taken two hours after injection of antigen and antibody in a reversed passive Arthus reaction in a rabbit. Note PMN infiltration in the vessel wall. Vascular damage is minimal at this early time.

tissues, the interaction of complexes with humoral and cellular elements of the host induce biochemical, pharmacologic, and morphologic events quite similar to those caused by other kinds of antigen-antibody reactions, such as the reactions of anti-tissue antibodies with their target tissues.

Experimental Lesions Induced By Immunologic Complexes

The Arthus phenomena. Pathogenically, the simplest complex-induced lesion is the Arthus^{18,19} reaction, a localized, acute necrotizing vasculitis. Essential to the full development of this lesion is the formation of relatively large amounts of antigen and antibody precipitates in the vessel walls.¹³ In order to so localize the reaction, one of the reactants, either antigen or antibody, must be in the circulation and the other injected locally. Early in the reaction, antigen and antibody diffuse toward each other, meeting and precipitating in the vessel walls (Figure 1). This antigen-antibody precipitate or complex, after its reaction with complement, is chemotactic for polymorphonuclear leukocytes (PMN), and within a few hours these cells infiltrate the involved vessels, which by now are undergoing necrosis (Figure 2). The PMN's phagocytize the antigen-antibody complex and appear to carry it away from the site of the reaction. Not only do the PMN's take up the complexes, but they are capable of degrading them rapidly, as shown in *in vitro* studies.²⁰

Serum sickness. More complex, but probably much closer to the immunologic situation in sys-

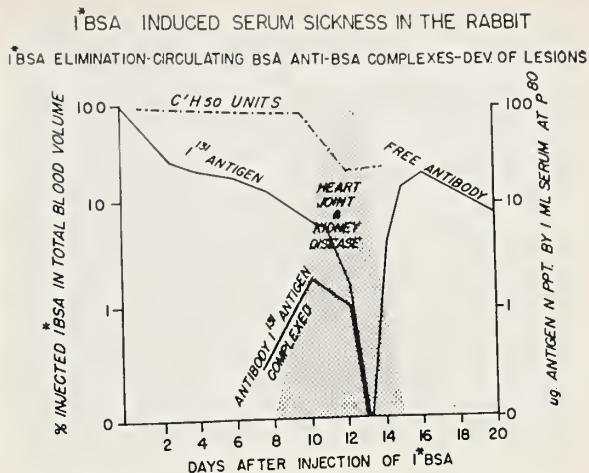


Chart 1.—Immunologic and morphologic events occurring after the injection of ¹³¹I-labeled bovine serum albumin into a rabbit in the dose of 250 mg/kg. Simultaneously with the appearance of detectable antigen-antibody complexes in the circulation, there is a drop in complement to less than half the normal value and the appearance of morphologic lesions in the heart, blood vessels, joints and kidneys. Shortly after the elimination of all antigen-antibody complexes, free antibody appears in the circulation and the inflammatory lesions of serum sickness rapidly disappear.

temic human disease than the Arthus reaction, is classic "one-shot" serum sickness. In this disease, either in experimental animals or in humans, a single large dose of foreign serum or purified serum protein is given to the subject. Chart 1 illustrates the relationship of most of the events that occur in this disease.⁸ The antigen level in the serum, in this case determined by following an isotopic label, can be seen to decline in three distinct phases. The first sharp fall results from equilibration of the intravenously injected foreign protein between intra- and extravascular serum protein pools. Next, there is a period of relatively slow loss caused by nonimmune catabolism of circulating free antigen at a rate characteristic for the particular protein injected and the recipient species. Finally, there is a phase of rapid loss just preceding the appearance of free circulating antibody. The antibody as it forms combines with the antigen in the serum at first in an extreme antigen excess environment predisposing to the formation of small complexes capable of remaining in the circulation as indicated by the first part of the complex line. As the amount of antibody formed increases, the antigen-antibody complexes become larger and are finally rapidly removed. Coincidental with the presence of antigen-antibody complexes in the circulation, there is a fall in the serum complement level and the appearance of acute inflammatory lesions in the kid-

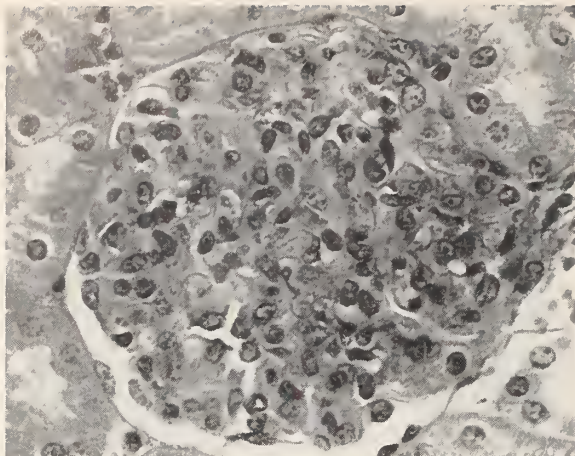


Figure 3.—Photomicrograph of a section of a kidney of a rabbit with serum sickness. This rabbit was sacrificed just prior to the elimination of all circulating complexes. The most striking abnormality is the occlusion of glomerular capillaries by proliferating endothelial cells and trapped leukocytes making the glomerulus virtually avascular. This morphologic change is comparable to that seen in acute proliferative human glomerulonephritis. Hematoxylin and eosin. $\times 475$.

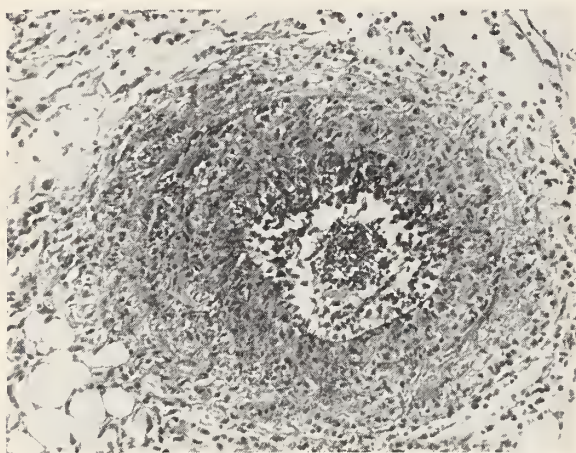


Figure 4.—Arterial inflammation in a coronary artery taken from a rabbit with acute serum sickness. A marked accumulation of PMN's is noted and abundant fibrinoid deposition in the media is apparent. Hematoxylin and eosin. $\times 200$.

neys (Figure 3), heart, arteries (Figure 4), and joints, strongly reminiscent of lesions of acute glomerulonephritis, rheumatic fever, lupus erythematosus, polyarteritis nodosa, and rheumatoid arthritis. These lesions vary in the degree to which the different cellular responses to antigen-antibody complexes participate, but prominent in most are endothelial proliferation, increased vascular permeability, and a variable PMN infiltration.

If, as has been postulated, these lesions are caused by the circulating complexes, it would be



Figure 5.—Fluorescent photomicrograph of a glomerulus similar to that in Figure 3. The section was treated with fluorescent anti-rabbit gamma globulin and reveals a granular deposit of this protein along what is undoubtedly the basement membrane. Host complement and the BSA antigen give a similar fluorescent pattern.

expected that the complexes should be found in the lesions. Presumptive evidence for this has been obtained by fluorescent antibody staining of antigen, host gamma globulin (Figure 5), apparently specific antibody and host complement in the cardiovascular and renal lesions. The substances were specifically concentrated in the lesions and appeared to be deposited coincidentally with their development. Additional support for the etiologic role of complexes in the cardiovascular and renal lesions was provided by Benacerraf and associates,²¹ and McCluskey and associates,²² who infused complexes into normal animals and produced arteritis, endocarditis and glomerulitis. While it cannot be determined whether the initial, local phlogogenic stimulus in serum sickness lesions results from systemic liberation of active humoral agents which act locally or by the fortuitous focal deposition of small amounts of complexes, it is likely that the accumulation of complexes from the circulation in the developing lesion, as a result of increasing vascular permeability, causes the snowballing inflammatory reaction. With the combination of all antigen into complexes and its subsequent elimination from the circulation, the inflammatory lesions in all sites rapidly resolve, and only occasional microscopic scars remain. It is the transitory course of conventional "one-shot" serum sickness that limits its usefulness as a model, either conceptually or practically, for the chronic progressive diseases, such as rheumatic fever, rheumatoid arthritis, the early stages of which it closely resembles.

TABLE 1.—Glomerulonephritis—Daily Injections

Antigen	Dose Range mg/day	No. of Rabbits Injected	Antibody Response		
			Ab excess	Equiv.	Ag excess
BSA	0.5 - 200	82	46 (2)	26 (22)	10
HSA	10 - 25	11	10	1 (1)	0
BGG	10 - 50	36	8	15 (15)	13
HGG	10 - 50	31	10	7 (5)	14
TOTALS		160	74 (2)	49 (43)	37

() Chronic Glomerulonephritis

If antigen-antibody complexes are involved in the chronic clinical entities mentioned above, it seems likely that experimental conditions designed to keep small amounts of such complexes present in the circulation for long periods of time should produce chronic progressive disease. Six years ago we extended earlier efforts to make such a model,²³ injecting intravenously small amounts of heterologous serum proteins daily into rabbits.¹⁷ As shown in Table 1, bovine serum albumin (BSA), human serum albumin (HSA), bovine gamma globulin (BGG) and human gamma globulin (HGG) all served as satisfactory antigens. The antibody responses to daily injection of these antigens were of three types: (1) *very large*, the animal having a large excess of antibody in the circulation at all times and no circulating soluble complexes; (2) *nonexistent*, in which case antigen in considerable amounts without antigen-antibody complexes was found in the circulation, and (3) *relatively small* in relation to the antigenic exposure, with the result that the antibody that was formed combined with the injected antigen in an antigen excess environment and formed soluble antigen-antibody complexes—these complexes persisting in the circulation for most of the interval between the daily antigen injections.

The diseases that resulted from the daily antigen-antibody reaction depended primarily on the relative amounts of antigen and antibody in the subject and little, if at all, upon the absolute amounts of antibody or upon the immunologic characteristics of the antigen. The rabbits making a vigorous response passed from an antigen excess environment to an antibody excess environment during the second week of injections and had at this time for a period of several days sizable amounts of antigen-antibody complexes in the circulation. As might be expected, where complexes were circulating, typical serum sickness with acute inflammatory lesions of heart, blood vessels, and kidney developed. As with "one-shot" serum sickness, the complexes were identifiable in the lesions.

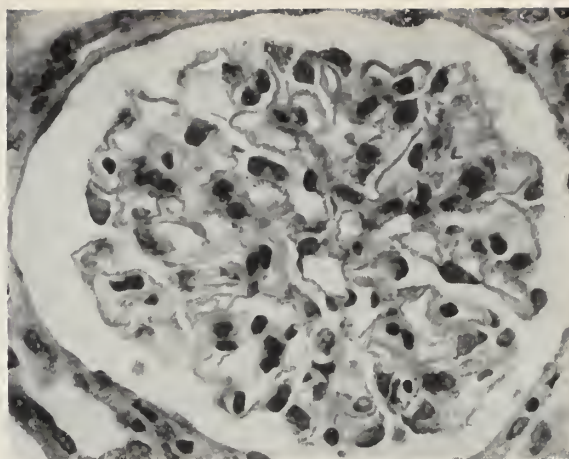


Figure 6.—Photomicrograph of a section showing membranous glomerulonephritis in a rabbit with circulating complexes as a result of daily injections of small amounts of antigen. Basement membranes of glomerular capillaries are noticeably thickened, but the number of endothelial and epithelial cells appears normal and the capillaries are widely patent. Hematoxylin and eosin.

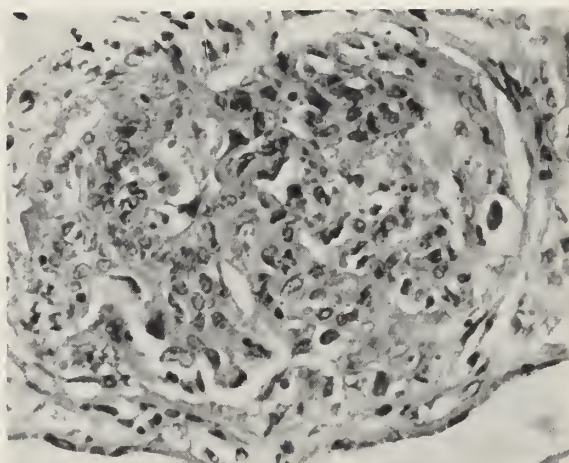


Figure 7.—Photomicrograph of a section from kidney of a rabbit having complexes in the circulation for several months as a result of daily antigen injections. This glomerulus shows proliferative changes with crescent and adhesion formation, increase in the number of glomerular cells and obliteration and lobulation of the glomerular capillaries. Hematoxylin and eosin.

As soon as the rabbit had made sufficient antibody to achieve permanent antibody excess, each injection of antigen was incorporated immediately into insoluble antigen-antibody aggregates and quickly removed from the circulation, and all evidence of disease disappeared. The rabbits making no antibody response had considerable amounts of antigen in the circulation at all times without any evidence of disease, a result indicating the lack of toxicity of antigen alone.

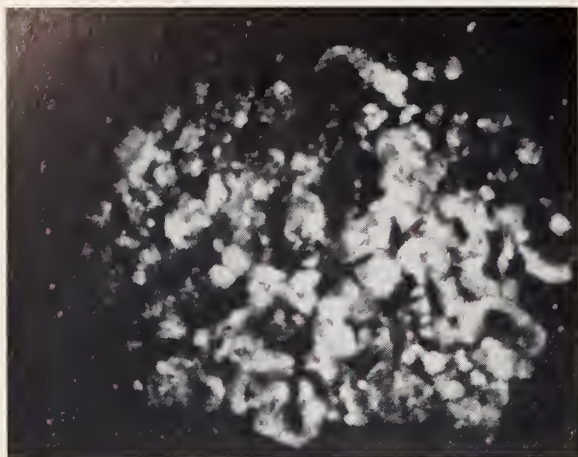


Figure 8.—Fluorescent photomicrograph of glomerulus from animal seen in Figure 6 stained for the injected antigen. The antigen is found in a lumpy deposit along the glomerular capillary walls. In spite of the high concentration of antigen seen in these glomerular capillary walls, there is little or no antigen elsewhere in the kidney.

It was among the animals making antibody responses too small to cause elimination of antigen but sufficient to result in the formation of circulating complexes that chronic progressive disease developed (Table 1). This pathogenic immunologic balance was achieved in some animals making little antibody with only 0.5 mg antigen per day and in some animals making much antibody with 100 to 200 mg antigen per day. After one or more months of injections and periods of one to several weeks during which antigen-antibody complexes were circulating most of each day, a progressive glomerulonephritis developed. In most rabbits, disease could be turned off or on by changing the dose of antigen. If the dose was either lowered to allow a continual antibody excess or raised to give a very large antigen excess, progression of disease stopped. If the dose was again returned to a level giving rise to soluble complexes, the disease progressed.

The chronic glomerulonephritis was detectable clinically by proteinuria, in some instances hematuria, hypoproteinemia and elevated serum cholesterol and urea levels. The most common and probably the earliest anatomic form of this disease was a membranous glomerulonephritis characterized by thickened glomerular capillary basement membranes with little or no endothelial proliferation. By morphologic criteria this lesion was much less inflammatory than degenerative. As the disease progressed, proliferative and scarring reactions became more evident (Figures 6, 7). Again, as

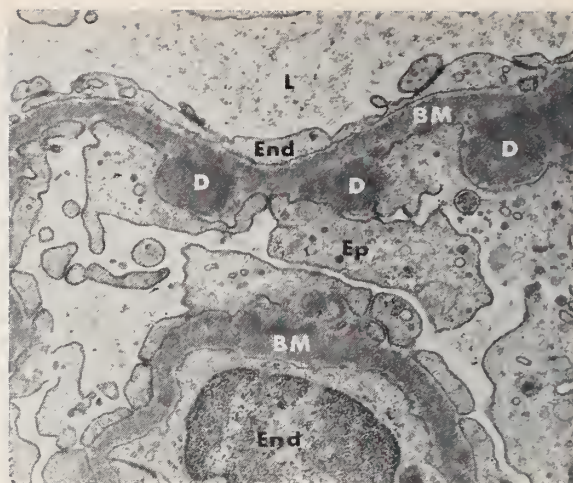


Figure 9.—Electron micrograph from kidney with membranous glomerulonephritis resulting from daily injection of antigen. Note lump deposition of electron-dense material (D) along the outer aspect of the basement membrane. Endothelial cells are relatively normal, while epithelial cells have lost their foot processes and attach continuously to the basement membrane. The lumpy dense deposits (D) along the outer aspect of the basement membrane correspond as closely as could be determined to the deposits staining positively for antigen, host globulin and complement as seen in the fluorescent photomicrographs. Photograph supplied by Dr. J. D. Feldman.

would be expected if the complexes were causing this renal lesion, antigen, host gamma globulin and host complement were found concentrated in the thickened basement membranes (Figure 8). By electron microscopy a lumpy, dense deposit was seen along the outer aspect of the basement membranes corresponding to the antigen, gamma globulin, and complement-rich deposits visualized with the fluorescent antibody technique (Figure 9). Subsequent electron microscope studies with ferritin-labeled antibody have confirmed this correspondence.²⁴ Once in this site, the immunologic reactants and the morphologically demonstrated deposits persisted for long periods—as much as one year after cessation of antigen injections—with persistence of associated renal malfunction.

Since the circulating complexes in either “one-shot” or “daily-injection” serum sickness bear no known immunologic relationship to the tissues which are injured, the factors predisposing certain parts of certain organs to injury by the complexes are apparently nonimmunologic. In the prolonged daily exposure to low levels of circulating complexes, the kidneys were the only organs injured, whereas in “one-shot” serum sickness with larger amounts of complexes present, heart, vessels and joints also suffered lesions. This vulnerability of

the kidneys in the presence of low levels of complexes may be related to the extensive renal blood flow and the normal filtering function of this organ. The exclusive concentration of complexes along the outer aspect of the basement membranes of the renal glomeruli is also probably determined by anatomic and physiologic peculiarities of the kidney. Some complexes apparently traverse the basement membrane but then are retained at its outer aspect or between the basement membrane and epithelial cells. It may be that as the complexes progress through the basement membrane, they tend to aggregate and become less soluble as a result of a reduction of excess antigen in the environment. Once here the complexes appear to be sequestered from circulating cells or tissue cells capable of degrading them. The coexistence of proteinuria with these deposits suggests that they interfere with the function of the basement membrane or epithelial cells or both. Some complexes also may be deposited on the inner aspects of glomerular capillaries or vessels elsewhere, but in these sites would be liable to removal by endothelial cells, PMN's or macrophages, and thus not accumulate. In "one-shot" serum sickness the development of lesions in joints, arteries and endocardium, as well as kidney, suggests that tissues involved in the filtration of blood are most susceptible to injury from circulating complexes.

Mechanism of Localization of Circulating Antigen-Antibody Complexes

In serum sickness, as noted above, the experimental evidence has indicated that the lesions result from the localization of circulating immune complexes. Since this may well be a common pathogenic mechanism in human disease, it is important to have an understanding of the ways in which the circulating complexes may localize in vessel walls.

Studies to date^{25,26} of the physiochemical properties of circulating soluble antigen-antibody complexes that govern their ability to localize in vessels subjected to increased permeability have indicated (1) that increased permeability of the vessel is necessary for localization to occur; (2) that there is no detectable affinity of soluble complexes for the basement membrane or "activated" endothelial cells; and (3) that the complexes and other macromolecules apparently localize because of their large size—that is, they are trapped along the basement membrane filter.

Further studies of acute immune complex disease in rabbits have suggested that similar mechanisms may be involved in the localization of circulating immune complexes. Carbon injected intravenously to serve as a marker during the onset of serum sickness was found to localize along the internal elastic lamina of large arteries in the early lesion sites.²⁴ When antagonists of vasoactive amines were administered in high doses just before development of the disease, complexes failed to localize and the lesions were largely inhibited. Depletion of the major source of vasoactive amines in the blood of rabbits—the platelets—had a similar effect. The treatment did not inhibit the formation and production of complexes. Surprisingly, glomerular localization of the complexes, glomerular lesions and proteinuria were also diminished by both antihistamine-antiserotonin treatment and platelet depletion. These data contrasted with the expectation that circulating complexes would localize on the glomerular basement membrane owing to the natural filtration already existing in the glomerulus. In the presence of vasoactive amines, a contributing factor influencing the localization of complexes in serum sickness was apparently the turbulence of flow.²⁴ Treatment with inhibitors or platelet-depleting agents did not prevent other immunologic reactions from developing, since nephrotoxic nephritis and Arthus reactions could be produced in animals similarly treated.

Platelets, which appear to serve a critical role in the localization of complexes in rabbits, have been shown to be decidedly affected by antigen-antibody complexes. In the presence of fresh serum, immune complexes cause clumping of platelets^{1,27,28} and release of histamine and serotonin.^{29,30,31} In addition, specimens of blood removed from rabbits undergoing serum sickness (presumably having complexes circulating) and examined rapidly while anticoagulated, showed clumping of platelets.³² These presumably had clumped in the blood stream before removal.

More recently the mechanisms by which immune reactions can liberate vasoactive materials from platelets have been examined.³³ Four possible processes were uncovered, the first three involving complement components. In the fourth mechanism, mononuclear cells from recently immunized rabbits are mixed with platelets and antigen in the absence of complement to bring about release of histamine and serotonin. A soluble factor is given off from the mononuclear cells that is prob-

ably responsible for the platelet changes. In acute immune complex disease in rabbits, complement components could be depleted with an anticomplementary factor, cobra venom. Despite complement depletion, deposition of the complexes occurred. The complement-independent mononuclear cell-platelet system was therefore examined in rabbits with acute immune complex disease. When antigen was mixed with the white cells and platelets of these rabbits, vasoactive amines were released from the platelets in 12 of 13 rabbits with immune complexes deposited in vessels and disease. In rabbits without disease and no deposition of complexes, the white cells of seven of eight rabbits failed to induce histamine release from platelets in the presence of antigen. Thus an excellent correlation was found between the presence of the mononuclear cell dependent histamine releasing mechanism and the deposition of circulating immune complexes in serum sickness of rabbits.

In summary, one may envisage the following scheme in the deposition of circulating complexes of antigen and antibody in acute immune complex disease in rabbits: sensitized mononuclear cells in the circulation in contact with antigen, probably through the intermediary of a soluble factor, induce clumping of platelets and release of vasoactive amines. The vasoactive amines bring about an evanescent increase in vascular permeability which allows large (greater than 19S) complexes in the circulation to deposit. The loci in vessels most susceptible to this reaction are points of greatest hydrodynamic force—for example, the branching points of arteries where platelets are known to impinge upon the vessel wall. Why the glomerulus is highly susceptible is not yet clear.

Mechanisms of Accumulation of Polymorphonuclear Leukocytes (PMN's)

Present concepts as to the mechanisms of accumulation of PMN's are based solely on the multitudinous studies of this process in general inflammation. These studies have demonstrated several important concepts, among which are: (1) There may well exist in areas of inflammation a humoral factor capable of attracting PMN's into the site of injury. While early evidence was inconsistent with this,³⁴ more recent studies employing micro foci of injury by Buckley³⁵ have been most indicative. (2) From *in vitro* studies there is some evidence that suggests a serum factor that may be important in the attraction of PMN's toward a site of tissue in-

jury.^{36,37} (3) From studies *in vitro* employing a wide variety of substances that are chemotactic, from washed bacteria to extracts of burnt tissue and serum, it would appear that there may be more than one substance capable of attracting PMN's chemotactically.

Studies on the attraction of PMN's to immunologic reactants in tissues have strongly implicated plasma complement as being essential for the generation of the chemotactic factor. Two reactions have been studied in detail, the Arthus phenomenon³⁸ and acute nephrotoxic nephritis.³⁹ Two approaches were taken, the first consisting of depleting animals of plasma complement (C) before the induction of reactions, and the second of using antibodies to induce reactions (in normal animals) that were incapable of fixing C. In both circumstances, PMN infiltration was absent, even though antigen and antibody deposits were detected in the vessel walls of Arthus sites or in the glomeruli of injected rats using fluorescent antibody techniques. In each case, however, little or no C3 (β_{1c} globulin) could be found in the vascular structure. Thus, in both C-depleted and normal animals with either Arthus reactions or acute nephrotoxic nephritis, a correlation existed between the ability of the antibody to fix C and the accumulation of PMN's at the antigen-antibody site (Table 2). These findings are in keeping with those of Bloch and coworkers,⁴⁰ who analyzed the biologic properties of guinea pig γ_1 and γ_2 7S antibody to a single antigen. The γ_1 fixed complement poorly and did not induce full Arthus reactions in homologous guinea pigs. The γ_2 antibody did fix complement and cause severe Arthus reactions.

Complement might bring about the accumulation of neutrophils in two ways: (1) through immune adherence and (2) by releasing chemotactic agents that cause a directional migration of neutrophils toward the point of greatest concentration—that is, the antigen-antibody complex where complement components are being activated.

Immune adherence is a phenomenon by which neutrophils and macrophages from most species, platelets from some species and erythrocytes of primates only, bind to an immune aggregate. In a few species the IgG antibody together with antigen is sufficient to induce adherence of the cells but in all species the fixation of complement, especially the third components, greatly augments the adherence. Presumably when immune complexes deposit or form in blood vessel walls and comple-

TABLE 2.—Effect of Complement Depletion on Polymorph Accumulation in Arthus Reaction and Early Nephrotoxic Nephritis

	No. of Rats	Polymorph Accumulation	Fluorescent Results		C'H ₅₀	Polymorphs (per mm ²)	Platelets
			C'	AgAb			
Nephrotoxic nephritis							
C-depleted	7	—	±	4+	< 7.5	10,960	—
Controls	6	+	3+	4+	38	4,200	—
Arthus							
C-depleted	10	—	±	4	< 8	7,300	591,000
Controls	5	+	3+	4+	49	4,300	610,000

ment through the third component is bound, neutrophils in the circulation would bind. This would be eliminated by depletion of c3, as was accomplished in the experiments noted above.

Much has been learned recently about the importance of complement in the formation of chemotactic factors. Using specially devised chambers, divided into two compartments by a micro-pore filter, neutrophil migration toward a concentration of chemotactic material can be measured at least semiquantitatively. A suspension of neutrophils is placed in the upper compartment and chemotactic factors are tested in the lower. Neutrophils migrate through the pores in the filter and may be counted on the bottom surface. Antigen and antibody, together with fresh serum, activate complement components and bring about migration of the neutrophils.^{41,42} Separation and identification of the complement components have implicated a complex of c5-6-7 as a primary chemotactic factor derived from the complement system. Once activated by c3, the c5-6-7 complex is rapidly released, forming a concentration gradient around the point of activation against which the neutrophils may migrate.^{42,43} More recently, a fragment of c3^{44,45} and of c5^{46,47} have been found to possess chemotactic activity for neutrophils. Thus in addition to the immune adherence mechanism imposed by c3, there are three chemotactic factors activated in the complement sequence that possess the capacity of bringing neutrophils to the site of an antigen-antibody reaction.

Mediation of Immune Complex Lesions

The foregoing discussion has analyzed the factors responsible for the vascular localization of potentially phlogogenic antigen-antibody complexes and PMN leukocytes. The following will describe the present knowledge of the host mediators that are responsible for the observed tissue damage. This work has been stimulated in the past several years by the elegant techniques of protein isolation

and characterization that are now available to the investigator. As a result, significant strides in this area have been made. Not only has knowledge been gained of the host factors that mediated the reactions, but a partial understanding has also been gained of the actual structures in the tissues that are damaged. At least in one instance, the damaged structure appeared to serve as a substrate for enzymatic attack. The mediators involved in this damage are both humoral and cellular. They include plasma complement and as yet poorly defined serum permeability substances, along with proteolytic enzymes and other permeability factors contained within cells. Mediators involved in the release of histamine by immunologic reactants are not discussed here.

Polymorphonuclear leukocytes (PMN's): their essential role in immune complex-induced tissue injury. The Arthus vasculitis is the first antigen-antibody induced lesion to be found dependent upon PMN's. Specific removal of PMN's by treatment with nitrogen mustard or heterologous anti-PMN sera has been shown to lead to striking inhibition of the reaction in several species.^{20,48,49,50} In depleted animals little or no evidence of injury was apparent macroscopically at eight hours, when normal reactions were at their maximum. Microscopically, there was no evidence of injury found in the vessel walls, even though deposits of immunologic reactants and complement had been readily demonstrated. By using dye-marked albumin (Evans' blue), however, it was apparent that a small amount of edema occurred in these reaction sites, suggesting some increase in vascular permeability despite the absence of PMN's. This was most readily demonstrated when large amounts of antibody and antigen were employed in passive reactions.

In a different immunologic disease, serum sickness of rabbits, when PMN's were removed just before development of the lesions, the usual necrotizing arteritis did not appear. Intimal proliferation was decidedly inhibited or absent, PMN

TABLE 3.—Proteinuria in First 24 Hours After Injection of Moderate Dosage of Nephrotoxic Serum

	Normal		Polydepleted	
	No.	mg/24 hours	No.	mg/24 hours
Rats	8	246	5	59
	6	50	7	6
Rabbits	5	1843	5	0.2

infiltration did not occur, and there was no destruction of the internal elastic lamina or fibrinoid necrosis in the arterial walls.⁵¹ The glomerulitis, normally seen in serum sickness, was not affected by PMN removal, but elimination of granulocytes may not have been achieved for a sufficiently long period.

Another immunologic disease of glomeruli is that of acute nephrotoxic nephritis. In this lesion, which is based on the reaction of injected antibody with the glomerular basement membrane, a clear role of PMN's also was apparent in the development of injury. Within two hours after the injection of antibody, a large accumulation of PMN's was observed in the glomeruli.³⁹ This accumulation lasted for about six hours and the numbers of PMN's found thereafter in the glomeruli diminished. Proteinuria was first detected when PMN's were accumulating and the numbers of PMN's in the glomeruli correlated well with the amount of protein in the urine. Removal of the PMN's, by using either purified anti-PMN antibody or nitrogen mustard, greatly or completely inhibited the occurrence of proteinuria (Table 3). Depletion of PMN's did not inhibit antibody and host complement binding in the glomeruli. As in the Arthus reaction, when large amounts of antibody were used, glomerular permeability increased in spite of the absence of PMN's. This indicated that factors other than those in PMN's could take part in the development of injury to the glomerulus. A similar immunologic permeability reaction was noted when antibodies to vascular basement membrane were injected intradermally. Both PMN-dependent and -independent reactions could be elicited in several species.

Vascular structures injured by PMN's in immunologic reactions. In attempting to analyze the various components of PMN's responsible for the damage of blood vessel walls during immunologic reactions, it was necessary to gain first an understanding of the specific structures within vessel walls that were damaged. In serum sickness,

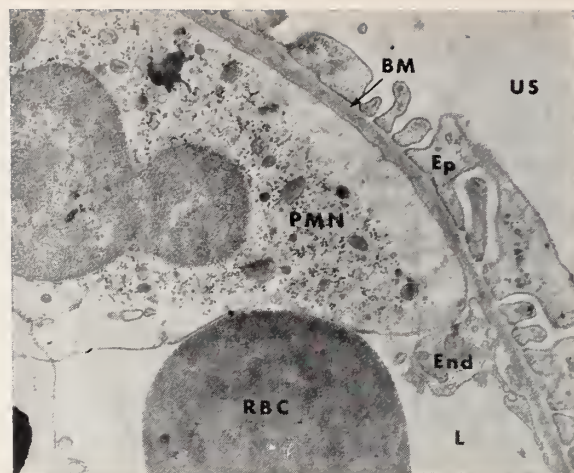


Figure 10.—Electron photomicrograph of a capillary loop taken from a rat 2.5 hours after an intravenous injection of nephrotoxic globulin. The endothelial cell (End) has been swept aside by the polymorph (PMN), leaving the basement membrane exposed only to the surface of the PMN. The polymorph has thus gained intimate contact with the basement membrane. US: urinary space; BM: basement membrane; EP: epithelial cell; RBC: red blood cell; L: lumen.

examination of the arteries revealed that upon influx of PMN's the internal elastic lamina was disrupted.⁵¹ This was shown by intravenous injections of carbon just before and during the time PMN influx was expected. It was found that up to the time of pronounced PMN infiltration, carbon accumulated in the arterial wall along the internal elastic lamina. As soon as PMN's emigrated into the site, microscopically visible damage to the internal elastic lamina occurred and carbon was found to pass freely into the media at that time. Damage to the elastic lamina did not occur in PMN-depleted rabbits.

In other PMN-dependent reactions, the vascular basement membrane apparently was a critical target structure. In the Arthus reaction, studies of the vessel wall during the influx of PMN's have revealed pronounced disruption of the basement membrane of the vessel wall.⁵² This was again shown by carbon leakage from the vascular lumen into the extravascular space during the influx of PMN's. The electron microscope also revealed destruction of the vascular basement membrane. Such damage did not occur in PMN-depleted animals of several species. In addition, in glomeruli, especially in acute nephrotoxic nephritis, morphologic evidence has suggested that the glomerular basement membrane is the site of primary injury.³⁹ As noted in Figure 10, PMN's forced aside the endothelial cells to gain intimate contact with the

underlying basement membrane. It was during this time that proteinuria commenced. Analysis of the urine during this acute phase has revealed basement membrane fragments that were released during the PMN attack.⁵³

The role of PMN leukocytic proteases in alteration of vascular basement membrane. In further considerations of the apparent attack of PMN's on basement membranes, it was found that lysates of PMN's or of the PMN cytoplasmic granules were capable of attacking semipurified glomerular basement membrane *in vitro*.⁵² These studies showed that peptides were released from the basement membrane by the PMN lysates as revealed by both paper electrophoresis and double diffusion precipitation reactions in agar. The reaction took place in the acid pH range only. Fractionation of the PMN lysates on DEAE cellulose and Sephadex® indicated that two proteolytic enzymes were responsible for the alteration of vascular basement membrane *in vitro*. From the pH optima and characteristic inhibition spectra, these two enzymes were found to be cathepsins D and E.⁵² Previous studies had suggested that granules of PMN's were capable of inducing hemorrhagic reactions when injected intradermally. Attention was drawn to the PMN hydrolases and their possible role in initiating such injury.^{54,55} In later studies, however, the purified hydrolases of PMN's were found not to induce immediate injury or delayed reactions upon intradermal injection in rabbits.⁵² Several investigators have found PMN cathepsins to be inactive at neutral pH's.^{52,56} Hence, one might look to factors other than the hydrolases in the production of tissue injury by direct injection of PMN fractions unless the injected material could bring about a fall in the local pH of the tissues. In the Arthus reaction, when large numbers of PMN's migrate into the vessel walls, thus entering into conditions that are anaerobic, sufficient lactic acid might well be produced to bring the pH into the range of activity of the catheptic enzymes. Any released cathepsins under these conditions could bring about damage to appropriate substrates in the tissue such as the basement membrane, and vascular damage would take place.

In human PMN's a neutral protease will hydrolyze isolated basement membrane much in the same way as the acid cathepsins of rabbit PMN's.⁵⁷ PMN's also contain a collagenase that may well attack basement membranes.^{58,59} More recently, an elas-

tase has been isolated that cleaves porcine elastin.⁵⁹ This may be the enzyme responsible for breakdown of the internal elastic lamina of arteries observed, for example, in serum sickness.⁵¹

The cationic proteins of PMN's. Aside from the catheptic proteases, at least four basic proteins have been isolated from the lysosomes of neutrophils that are capable of increasing vascular permeability. The effect of one of these follows its action on mast cells and the consequent release of histamine.⁶⁰ The other three act independently by means as yet unclear.⁶¹

Immunologic Injury of Blood Vessels Unrelated to PMN's

Mild injury to blood vessels as revealed by an increase in permeability has been demonstrated in Arthus reactions in the absence of PMN leukocytes. Amounts of antibody over 100 µg Ab N were required to induce this permeability reaction. Even more demonstrative of this phenomenon is the increase in permeability brought about by cutaneous injections of antibody to glomerular basement membrane in the absence of PMN's. This latter reaction is apparently the cutaneous counterpart of the PMN-independent immunologic injury to glomeruli that results in proteinuria.³⁹

Attempts have been carried out to find if complement is involved in the generation of this permeability factor. Animals depleted of complement using heat-aggregated gamma globulin were injected and given Arthus reactions with large doses of antibody and antigen. Similarly, normal animals were injected intracutaneously with noncomplement-fixing duck antibody to glomerular basement membrane.⁶² In each case, injury to the cutaneous vessels occurred despite the lack of complement fixation. Similarly, when large doses of nephrotoxic serum were injected into complement-depleted rats, proteinuria still occurred.⁶³ Undiminished reactions were also found in PMN-depleted C6-deficient rabbits and C5-deficient B 10 D2 old line mice. Hence, it would seem unlikely that the lytic action of complement was involved in the permeability reaction. In addition, a role of complement-mediated release of anaphylatoxin would appear unlikely in view of the normal permeability reaction developing in complement-depleted animals, and since treatment of rabbits with large doses of antihistamine (chlorpheniramine maleate) failed to inhibit the permeability reaction.⁶² Work involving the release of a permeability factor

from fresh serum by immune precipitates is being carried out in several laboratories and should contribute significantly to this area in the near future.

Immune Complexes in Human Diseases

The extent of the role of antigen-antibody complexes in the pathogenesis of human disease is not yet clear. However, in entities such as lupus erythematosus, glomerulonephritis, rheumatoid arthritis, Sjögren's disease, the immunologic vasculitides, idiopathic pulmonary fibrosis, serum sickness, and related drug reactions, infectious diseases such as subacute bacterial endocarditis and Aleutian disease in mink and, finally, some of the gamma globulinopathies, there is considerable evidence for the presence of antigen-antibody or gamma globulin-containing complexes in the circulation. In addition, the kinds of lesions attributable to antigen-antibody complexes in experimental situations are similar to those seen in many of these human diseases and support the suspicion that complexes may well be at work in the latter. Some of the features of these clinical diseases most closely related to experimental complex-induced lesions are discussed below. While ideas of how antigen-antibody complexes once they are formed may cause injury are rapidly becoming clearer, our knowledge of the antigens participating in complex formation or of the events responsible for the formation of the antibodies involved is still fragmentary at best. It is in these areas that, we may hope, our next advances will come, since this information will be essential not only to complete our understanding of this process, but also to provide means of preventing or manipulating it.

There are certain inroads into the obscurity surrounding the pathogenesis of glomerulonephritis and vasculitis. In glomerulonephritis, experimental evidence has indicated that when circulating immunologic complexes deposit in glomeruli and induce acute or chronic lesions, the immunohistochemical and ultrastructural appearance of the glomerulus is strikingly similar to that in acute or chronic glomerulonephritis and the glomerular lesions of Henoch-Schonlein^{17,64,65,66} purpura and systemic lupus erythematosus. In glomeruli of experimental acute serum sickness and human poststreptococcal glomerulonephritis, a hazy, poorly defined deposit is noted lying between endothelial cells and the basement membrane. Swelling of endothelial cells and PMN infiltration are also observed. By immunohistochemical techniques, in

acute serum sickness, antigen, antibody and complement usually are found in a granular powdery deposit along the basement membrane. In acute human poststreptococcal glomerulonephritis, early biopsy studies have revealed an exact replicate of these findings.^{67,68} Further, fluorescent studies have revealed streptococcal antigens in the affected human glomeruli,⁶⁷ although the pattern of fluorescence does not follow the basement membrane.

Taken together, these results offer compelling although not definitive evidence in favor of an immunologic inciting mechanism in acute human glomerulonephritis. In addition, the granular appearance of the gamma globulin and complement in the human lesions suggests that circulating complexes had deposited along the basement membrane or that an autoimmune reaction was taking place involving antigens unrelated to (or in addition to) those in the basement membrane. This latter possibility would have to be invoked, since a granular, non-linear, deposition of gamma globulin and complement was found in the human lesions quite unlike the linear, smooth deposition observed in nephrotoxic nephritis, in which antibody is known to react with glomerular basement membrane. In chronic experimental serum sickness nephritis, evidence has shown that when circulating complexes deposit in glomeruli over a prolonged period of time, large lumpy deposits that are rich in antigen, antibody and complement form along and on the epithelial side of the basement membrane.¹⁷ These deposits have a decided similarity to those in many cases of chronic glomerulonephritis in man.^{64,66} In the glomerulitis of lupus erythematosus, lumpy deposits have been found along the outer layer of the glomerular basement membrane. In the wire loop lesions of the glomeruli, c3 and c4 were found associated with γ G-globulin.⁶⁹

Of note is a recent clinical observation in patients with lupus erythematosus in whom free anti-DNA was detected in the circulation. The level of anti-DNA was noted to fall, and after its disappearance free DNA made its appearance.⁷⁰ Exacerbation of the disease was noted during the period of change from circulating anti-DNA to DNA. Immune complexes were not measured, but a correlation between complex formation and severity of glomerular disease should yield most interesting data in relation to that known from the serum sickness experimental model.

Other clinical diseases exist in which vascular

inflammation appears to have a recognizable inciting agent. Such is the case in hypersensitivity angitis developing after contact with sulfonamides, penicillin, and formalin.⁷¹ The foreign materials have not been identified as yet in lesions, and soluble complexes have not been detected in the circulation. Thus, a mechanism of serum sickness type cannot yet be invoked. In addition, no known common antigens have been demonstrated linking these foreign substances with human blood vessels; and the possibility that they alter natural molecules in the patient, conveying antigenicity to them, remains obscure. Therefore, while an immunologic inciting mechanism appears reasonable in hypersensitivity angitis, the process involved is uncertain.

In arteritis and vasculitis of various human lesions, morphologic findings also show a striking resemblance to the known models of immunologic vasculitis. In rheumatoid arthritis, one of the first human diseases in which complexes of γ G- γ G and γ G- γ M complexes were found,⁷² a striking arteritis has been found, similar to that seen in serum sickness. In meticulous three-dimensional studies of the earliest lesions in the subcutaneous connective tissue, Sokoloff⁷³ found an acute inflammatory arteritis to be the central feature. Acute cellular infiltration, necrosis, and disruption of the lamina elastica were all noted in the arterial wall. This latter finding is of interest in that the same observation of PMN-induced rupture of the lamina elastica was made in serum sickness arteritis, where it appeared to be the deciding event in the spread of inflammation from the intima into the surrounding media and adventitia.⁵¹ It is also of note that concentrations of gamma globulin have been found in rheumatoid nodules.⁷⁴

In the vasculitis of lupus erythematosus^{69,75} and polyarteritis^{76,77} γ G globulin and complement have been found in the lesions. In addition, the observation that heterologous complement binding occurs *in vitro* in such diseases as membranous glomerulonephritis⁷⁸ and the arteriolar and glomerular lesions of lupus erythematosus^{69,79} suggests that either immunologic reactants or aggregated gamma globulin molecules have localized in the vessel wall. A possible source of the gamma globulin is the plasma, since globulin-globulin complexes have been found in the circulation of experimental animals^{80,81,82} and in man.^{72,83} In man, at least, the amount of these complexes increases with age,

owing probably to the repeated immunogenic experiences of the individual.

Despite these many similarities between human lesions and the experimental models, their common pathogenic origin is still conjectural. Proof of a complex origin of the human diseases will require identification of each antigen and antibody in the lesion site, together with a close correlation between the appearance of complexes in the circulation and development of lesions.

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MEDICAL STAFF CONFERENCE

Von Willebrand's Disease

Distinction from Other Syndromes Associated with a Long Bleeding Time, and from Hemophilia

DR. NAGEL:* The patient is a 43-year-old Mexican-American man who was admitted to the Fort Miley Veterans Administration Hospital, San Francisco, on referral from the Veterans Administration Hospital at Fresno for evaluation of hypercalcemia. The patient had had numerous episodes of minor epistaxis in early childhood, but the first major episode of bleeding occurred at the age of 15 following tonsillectomy. Subsequently bleeding difficulties followed a number of surgical procedures. He gave no history of intradermal hemorrhage, hemarthrosis, or gastrointestinal or genitourinary bleeding. One brother gave a similar history of bleeding. In the patient's past medical history the only item of note was bronchial asthma since age 18. Asthma became progressively worse in later life and because of it he had had to quit working six years ago. During a stay in hospital in April of 1968 for bronchial asthma, the patient was noted to have hypercalcemia which was unresponsive to low calcium diet and oral prednisone.

On physical examination at the time of admission to the University of California Medical Center, the patient's blood pressure was 138/90 mm of mercury, pulse rate 80, weight 242 pounds and height 6 feet 1 inch. He was in no apparent distress. Examination of the head, eyes, ears, nose, and throat revealed only a distorted nasal septum

and a questionable tender mass over the left lower pole of the thyroid gland. On examination of the chest poor excursions, decreased breath sounds and scattered wheezes were noted. The heart sounds were diminished and the rhythm irregular. The abdomen was obese and without palpable organomegaly. No petechiae or areas of ecchymosis were evident.

Laboratory data from the Veterans Administration Hospital included a hematocrit of 39 percent, a white count of 4,900 per cu mm with platelets of 178,000 per cu mm. Duke bleeding time was 2 minutes (normal). Prothrombin time was 100 percent. Clotting time (Lee and White) was 12 minutes and 18 minutes on two separate occasions. Calcium was 12.2 mg and phosphorus 2.1 mg per 100 ml. Creatinine was 1.0 and a serum protein electrophoresis was described as being normal. The patient was referred for additional laboratory studies (Table 1). Platelet adhesiveness was 19 percent (low) and the partial thromboplastin time was 70.8 seconds with a control of 41.

The thromboplastin generation time is of interest in that the absorbed plasma of a normal person corrected this patient's deficiency. As you recall, absorbed plasma contains Factor V, VIII, XI, and XII. The specific assay for Factor VIII disclosed a level of 6 percent.

X-ray examination disclosed nothing of pathological significance.

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TABLE 1.—Hemostatic Studies on Patient

Bleeding time (Ivy).....	2 minutes
Platelet count.....	280,000 per mm ³
Platelet adhesiveness (Salzman).....	19%
Prothrombin time (Quick).....	77%
Partial thromboplastin time.....	70.8" (control: 41.0")
Thrombin time.....	11.4" (control: 11.7")
Whole clot lysis.....	none
Clot retraction.....	normal

Thromboplastin generation test:

Absorbed Plasma	Serum	Minutes of Generation		
		2	4	6
normal	normal	>60"	15.7"	10.9"
patient	patient	>60"	>60"	>60"
patient	normal	>60"	>60"	53.0"
normal	patient	>60"	33.7"	11.0"

Specific coagulation factor assays:

Factor II (prothrombin).....	plasma 106%	serum 5%
Factor VIII (AHF).....	6%	

DR. FUDENBERG:* This patient will be discussed by Dr. Herbert Perkins, who has had a long sustained interest in hemophilia and von Willebrand's disease. We will ask him to tell us about the factors necessary for diagnosis and also what therapy to use.

DR. PERKINS:† I get invited every few years to discuss von Willebrand's disease at these rounds. These repeated invitations result, I am sure, because inadequacies of the diagnostic tests employed and differences of opinion about classification of this and related defects leave the audience somewhat confused as to the exact criteria for definite diagnosis. The patient just presented offers an excellent illustration of the kind of diagnostic dilemma which may occur and how it may be resolved. Let me begin by saying that I use the term "von Willebrand's disease" to describe a congenital bleeding diathesis occurring in both sexes with a dominant inheritance and characterized primarily by bleeding from mucous membranes with the laboratory hallmarks of a prolonged bleeding time, decreased adhesiveness of platelets to glass, and a somewhat reduced level of Factor VIII, the anti-hemophilic factor (AHF). Von Willebrand's disease is characterized, in addition, by two rather unexpected findings. Although the defect seems to involve formation of the platelet plug, correction of the abnormal bleeding time is accomplished with transfusion of plasma and not with platelets.¹ In addition, transfusion of a variety of plasma derivatives results in a progressive rise in the Factor

VIII level of the recipient to levels far higher than can be accounted for by the amount of Factor VIII transfused.

The confusions about von Willebrand's disease and the differences of opinion about classification arise from multiple sources. First, these patients tend to have borderline abnormalities in hemostatic tests. Clinically their bleeding is more likely to be a minor nuisance than presenting as a serious emergency for management of hemostasis. The borderline results of tests explain why abnormal answers may be obtained on one occasion; normal ones on the next. Moreover, the tests employed are quantitatively rather poorly reproducible, and I shall have more to say on this subject later. Finally, the type of bleeding seen in von Willebrand's disease and its association with a prolonged bleeding time are found in a number of other conditions, both congenital and acquired. Some authorities use the term "von Willebrand's disease" to include a wider spectrum of congenital bleeding syndromes than I have defined, considering it a "waste basket" with a variety of mechanisms involved.

A further complication in our understanding of von Willebrand's disease results from the fact that the *in vivo* evidence already mentioned,¹ which indicates that we must be dealing with a deficiency of a factor contained in the plasma, is not yet corroborated by any good *in vitro* evidence. It is currently believed that the first step in formation of a platelet plug is a specific attraction of platelets to exposed collagen fibers. Adenosine diphosphate (ADP) is then released, resulting in platelet aggregation. This last step requires calcium and one or more plasma cofactors.² This scheme would corroborate our *in vivo* evidence if we could identify the factor we transfuse into these patients to shorten their bleeding time with the plasma cofactor of ADP aggregation. Unfortunately, none of the *in vitro* evidence seems to point in this direction²; in fact, fibrinogen seems to be at least one of the necessary plasma cofactors. This is a confusing point for which we have no good answers at the moment.

I would like now to discuss the diagnostic tests we use and the problems they create. The bleeding time determination is too often done in routine laboratories with a variety of implements that make incisions of varying depth and width. Under these conditions results are almost totally meaningless. Close reproducibility is difficult to obtain even with acceptable, well-standardized tests. The method of Duke (favored by hospital laboratories because

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TABLE 2.—*Related Data on Five Members of a Family In Which Three Had History of Bleeding*

	Age	Bleeding History	Bleeding Time	Factor VIII	Platelet Adhesiveness
Propositus	54	yes	30'	29%	0%
Son	33	yes	30'	28%	0%
Son's wife	36	no	5.5'	85%	47%
Granddaughter	10	no	2.5'	65%	52%
Grandson	8	yes	6'	36%	0%

of speed and simplicity) is not as sensitive as the technique of Ivy in which standard incisions are made in the forearm after application of a blood pressure cuff inflated to maintain a pressure of 40 mm of mercury. Nilsson and coworkers³ demonstrated that patients with von Willebrand's disease and a prolonged Ivy bleeding time will, in approximately half of the cases, have a normal result with the Duke test. The Duke bleeding time will thus detect only the more severe cases of von Willebrand's disease. Although this will result in identification of the patients most likely to have serious clinical problems with hemostasis, the lesser sensitivity compared with the Ivy test explains some of the discrepant conclusions in the published literature. With either method borderline bleeding times may be encountered, and such patients may demonstrate an abnormality one time and not the next.

Published reports^{4,5} of studies of families with von Willebrand's disease often point out the inconsistency of results among different involved members of the same family. Genetic mechanisms such as variable penetrance are often invoked as an explanation, but I believe that at least some of these differences may be attributed to the variability of our test results. Table 2 shows the data in one of our family studies. The propositus and his son and grandson clearly appear to share the defect. All results are classical for von Willebrand's disease except for normal bleeding time in the grandson. One could interpret this as variable penetrance; but this test was done only once, and I am more inclined to attribute it to variability in the laboratory test.

The Factor VIII assay also leads to trouble. Early reports on von Willebrand's disease emphasized the distinctive value of this test because its degree of reproducibility is excellent. Unfortunately, the levels encountered in von Willebrand's disease are again frequently in the borderline range.⁶ Normal levels of Factor VIII extend from 50 to 200 percent of the mean; in von Willebrand's disease they are often in the 30-50 percent range.

This leads to erroneous conclusions for two reasons. First, levels of antihemophilic factor rise with stress, and they do this in von Willebrand's disease as they do in normals. Often the initial blood sample is taken at a time of acute stress when the Factor VIII level has climbed into the normal range. The true deficiency can be established only later when baseline conditions are achieved. A second source of difficulty with borderline results is that a single sample may be reported as having 40-45 percent Factor VIII in one laboratory and 50-55 percent in another because of the simple fact that the standard Factor VIII preparations used as a criterion of 100 percent activity are not identical in the different laboratories.

The platelet adhesiveness test of Salzman has added further diagnostic help, but again further confusion. The test is performed by determining the loss of platelets after passage through a standard glass bead column directly from the blood stream into a tube with EDTA anticoagulant. Normally 26 to 60 percent of platelets are trapped by the column. The percent adhesiveness result thus obtained is the difference between two platelet counts. A glance at the table on page 54 of George Cartwright's book *Diagnostic Laboratory Hematology*⁷ will convince you that a test which depends on the difference between two platelet counts cannot be highly reproducible in a quantitative sense. We have never found it reproducible enough to use as a test for monitoring the effect of therapy. We have, however, found it effective to a significant degree in distinguishing patients with von Willebrand's disease from normal persons. Our unpublished studies on 50 normal subjects demonstrated that there were 15 percent who had platelet adhesiveness values on a single occasion below the 26 percent accepted as the lower limit of normal; however, 79 percent of patients with von Willebrand's disease had abnormally low results. The differences are significant enough so that this test (in combination with other tests) helps to distinguish von Willebrand's disease, but the extent to which results in normal persons and affected patients overlap explains some of the confusion in published reports. Incidentally, the degree of overlap just mentioned coincides very closely with that obtained by a number of laboratories in an international cooperative study, as reported by Salzman⁸ at a recent meeting of the National Hemophilia Foundation.

Turning from the problems created by the in-

adequacies of our diagnostic tests, I would now like to discuss clinical entities which may be confused with von Willebrand's disease. First, I would like you always to keep in mind that these include two rather common acquired defects. I am talking, of course, of uremia in which a qualitative platelet defect is the major cause of the prolonged bleeding time and of the dysproteinemias (especially macroglobulinemia) in which coating of platelets by the abnormal protein explains the defect. A closely similar condition can also be produced by transfusion of excessive amounts of dextran. These acquired conditions are distinguishable from von Willebrand's disease with relative ease.

We are still left with a large group of illnesses, which by history appear to be congenital, which should be distinguished from von Willebrand's disease because specific therapy required may not be the same. First to be considered are the qualitative platelet defects. In these there is usually a normal number of platelets, but their function is impaired. Traditionally these states have been classified into two groups: thrombasthenia, characterized primarily by a defect in clot retraction, and thrombocytopathy, which entails a failure to make the platelet phospholipid (factor 3) available for coagulation. As more patients have been studied, the distinction between these two categories of qualitative platelet defects has tended to become blurred. In some patients both types of abnormalities are demonstrated.

A qualitative platelet defect may be suspected initially from the appearance of platelets on the blood smear. Large, bizarre platelets with no tendency to clump may be seen. A second simple clue may come from failure of the clot to retract. This is one reason why this test should be included in routine hemostatic studies of bleeding patients. The prothrombin consumption test is a good indicator of the availability of platelet factor 3. More commonly used coagulation tests, such as the partial thromboplastin time, do not indicate platelet defects; platelet substitute is always provided in the form of cephalin. Other techniques which have been used to test the availability of platelet phospholipid for coagulation include the thromboplastin generation test (employing washed platelets of the patient) and incubation of platelet-rich plasma with kaolin. We find prothrombin consumption the simplest approach. We confirm the role of platelets in any defect demonstrated by showing that prothrombin consumption is normal-

ized with added platelet substitute, following the suggestion of the Mayo Clinic group.⁹

The simple tests thus far discussed do not begin to take advantage of the sophisticated knowledge of platelet function which is exciting much attention nowadays. There are ways of testing the various phases of the mechanism of formation of the platelet plug, to which I have already referred. One can test for platelet affinity to collagen, for platelet responsiveness to ADP and other substances. Dr. Paul Aggeler's laboratory has experience with a battery of such tests.¹⁰ With their aid, cases which superficially look very much like von Willebrand's disease may be established as having a qualitative platelet defect. So far as we know at the moment, however, these qualitative platelet defects make up a very small proportion of the long bleeding time syndromes I am discussing. The major definable group has von Willebrand's disease. There remain, however, a sizable proportion of patients with long bleeding times, normal Factor VIII levels, and (as yet) no defined qualitative platelet defect. Others with similar histories manifest various combinations of normal and abnormal results in the bleeding time, AHF assay, and platelet adhesiveness test. If bleeding is a serious problem in such a case, it may become necessary to determine by trial and error whether plasma (or its cryoprecipitate derivative) or platelets will correct the abnormal bleeding time. I should emphasize, however, that most of these patients do not have serious enough problems to justify transfusions even when surgical operation is contemplated.

Enough has been said to make it clear that it may at times be difficult to distinguish between von Willebrand's disease and mild hemophilia. The case under discussion today represents an example of this difficulty. The family history occasionally helps if the pattern of inheritance is clear. Our patient today had only one relative with a history of bleeding (his brother). This could be consistent with either disease. Bleeding was primarily from mucous membranes, with many nosebleeds as a child. There was no serious problem until age 15 when he bled abnormally after tonsillectomy. A later spinal operation was not associated with excessive blood loss. The platelet adhesiveness was 19 percent. All of these facts suggested that von Willebrand's disease is most likely. On the other hand bleeding time was normal, and the only involved relative was also a male. Hemophilia thus remained a definite possibility.

The diagnosis in this instance was of far greater importance than satisfying academic curiosity. The patient, already a serious operative risk, needs parathyroidectomy, and defective hemostasis in this area of the neck following operation could not be tolerated. We believed the importance of accurate diagnosis justified transfusion of an AHF concentrate to permit a conclusive diagnosis. Such trials are not loosely recommended because of the risk of inducing hepatitis.

The distinction between hemophilia and von Willebrand's disease can usually be established because the patient with hemophilia has a rise in AHF level to the point expected based on the amount of Factor VIII transfused and the plasma volume of the patient in which it is diluted. Peak values occur immediately, followed by curvilinear decay with a half-life of about ten hours. In contrast, the patient with von Willebrand's disease may, shortly after transfusion, have a Factor VIII level somewhat higher than expected, followed by a progressive *rise* for 24 to 48 hours.

Our patient was given 8 units of cryoprecipitate. His Factor VIII jumped to an immediate peak of 18 percent (almost identical with the predicted 17 percent) and then fell. Subsequent values plotted on semilogarithmic paper fell in a straight line with a half-life of 16 to 18 hours. The first gain from this test, then, was proof that he had classical hemophilia. Second, the rate of decay (somewhat slower than average) clearly proved he had no circulating anti-coagulant which might destroy transfused AHF. Third, we could now predict with considerable confidence how much Factor VIII it would take to raise this patient's level to any concentration we desired. We knew how much Factor VIII activity we had administered, and we knew how high that raised his level.

The fourth bit of information was unexpected: a very severe case of hives developed. Since we have had previous experiences in which severe allergic reactions resulting from transfusions were due to an antibody in the patient's serum reacting with a foreign type of IgA immunoglobulin in the donor plasma,¹¹ we had Dr. Vyas* test the patient's serum. Anti-IgA was found. We could not plan operation for this patient knowing that he might have an allergic reaction to the Factor VIII concentrate we were using, which might force us to interrupt therapy.

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I have emphasized the importance of an exact diagnosis when control of bleeding by transfusion is required to permit operation, because it may dictate our choice of product for transfusion. The Factor VIII level of a patient with von Willebrand's disease is relatively easy to raise and can be maintained with relatively infrequent transfusions. It may be necessary, however, to correct the bleeding time also. I have mentioned that this may be accomplished by transfusion of plasma, but very large volumes are required.

Fortunately, cryoprecipitate (the Factor VIII concentrate which may be prepared in the blood bank) is an effective concentrate of the factor which corrects the bleeding time. Many of you remember a patient with von Willebrand's disease in this hospital who bled repeatedly and massively from the gastrointestinal tract.¹ His bleeding time was longer than 30 minutes, but his antihemophilic factor was usually in a range which should not have resulted in impaired hemostasis (40 to 45 percent). Three attempts to control gastrointestinal bleeding surgically resulted only in an increased rate of hemorrhage. The patient's bleeding time could be shortened by cryoprecipitate, but it required at least eight units in this 70 kg man, and even then the degree of shortening was often not into the normal range. It was enough, however, to achieve temporary control of hemostasis. Thus, cryoprecipitate is the recommended form of transfusion therapy for patients with von Willebrand's disease. Commercial Factor VIII concentrates so far tested do not contain the highly labile factor which corrects the bleeding time. This is obviously one important reason why we must distinguish between von Willebrand's disease and hemophilia. If hemophilia is present, commercial concentrates may be used (Table 3).

I have tried to present some of the problems we face in trying to differentiate between hemophilia and the various bleeding syndromes associated with a long bleeding time. In our experience, von Willebrand's disease has been just as common as hemophilia, and these two conditions are by far the two most common congenital bleeding diatheses. The relative frequencies reported from different laboratories differ depending largely on the criteria they use to diagnose von Willebrand's disease.

DR. FUDENBERG: Dr. Aggeler, would you mind opening the discussion?

TABLE 3.—*Factors in Differential Diagnosis of von Willebrand's Disease*

	<i>von Willebrand's Disease</i>	<i>Hemophilia</i>	<i>Qualitative Platelet Defects</i>
Bleeding time	Increased	Normal	Increased
Platelet adhesiveness	Decreased	Normal	Normal or decreased
Factor VIII	0-50% (often 30-50%)	0-30% (often <1%)	Normal
Response to transfusion of Factor VIII	Immediate rise to expected or higher level with further progressive rise for 24-48 hours	Immediate rise to expected level, then exponential fall with half-time of 10-16 hours	
Prothrombin consumption	Usually normal	Usually poor (not corrected by platelet substitutes)	Normal or poor (corrected by platelet substitutes)
Clot retraction	Normal	Normal	Normal or poor
Bleeding time corrected by transfusion of	Fresh plasma or cryoprecipitate		Platelets

DR. AGGELER:* I would just like to make some very minor remarks that might help to clarify some of Dr. Perkins' problem cases. One is that aspirin might have a greater effect on the bleeding time in abnormal cases; although, it does have an effect on the bleeding time in normal people too. In an equivocal situation one might be able to bring out a slightly prolonged bleeding time by giving aspirin and checking it two hours later.

I would like to discuss briefly the work of Dr. Sahud¹⁰ to clarify the relationship between aspirin, a type of thrombasthesia, and von Willebrand's disease. There is a type of thrombasthenia, fairly rare I think, that has entirely normal levels of AHF associated with prolonged bleeding time and decidedly impaired platelet adhesiveness. In these patients platelet aggregation tests can be shown to react quite normally to the higher concentrations of ADP, but the platelets do not adhere to collagen fibers, nor are they aggregated by collagen suspensions. This group of patients is obviously very important to identify, since we would want to treat with platelets and not with cryoprecipitate.

The other area in which confusion arises is in the use of "the pill" or in pregnancy where AHF levels may rise (in a pregnant patient particularly). The patient with a baseline level of AHF of 25 percent may have 50 percent (in the last trimester of pregnancy) and the diagnosis of von Willebrand's disease may be missed. The role of "the pill" in raising AHF is a little less clear. If a patient is in mid-cycle; that is, when she has taken "the pill" for a couple of weeks, one may get some rise in AHF level. At the beginning or end of the cycle the rise is apt to be less prominent.

QUESTION: What happened to the patient, particularly with respect to his requirement for surgical operation?

DR. PERKINS: He is still waiting for a final decision. I am hopeful we may find some way to avoid operating. I think we have an almost impossible situation—neck dissection needed in an asthmatic, obese, hemophiliac patient, who might react so violently to transfusion therapy that it alone could kill him. I just don't have any good answers to this. If the issue is forced and we are told, "This man will be dead in another six months if operation is not done," we may have to act. Our plan for the moment is to give him the new Hyland Method 4 concentrate, which is a very highly concentrated Factor VIII. We hope that it may be quite deficient in iga. The volume required to be transfused is very small. That will at least take care of the transfusion reaction problem, and we hope meantime that he can try to reduce the patient's weight and improve his lungs by stopping smoking.*

DR. SALMON:† Have you considered preparing some cryoprecipitate from a donor who lacks iga?

DR. PERKINS: Yes, that would be a good suggestion provided we could find such a donor who wouldn't mind being plasmaphoresed. We could collect many units from a single donor this way. I think we can get around this problem. The other one, the risk of operation, is more serious. The procedure on the neck demands that we achieve normal hemostasis, and this means a very large amount of Factor VIII concentrate. I calculated

* Paul M. Aggeler, M.D., Professor of Medicine.

* The Hyland Method 4 concentrate has been tried, and the patient has had no reaction.

† Sydney E. Salmon, M.D., Assistant Clinical Professor of Medicine.

that he will need approximately 32 to 36 units of cryoprecipitate to raise the Factor VIII level to 60 percent and then half that dose every 12 hours for 10 days. This would be the absolute minimum. That is a lot of antihemophilic factor concentrate.

QUESTION: Do corticosteroids inhibit bleeding in von Willebrand's disease? They do in thrombocytopenia.

DR. PERKINS: The reason that bleeding is helped in thrombocytopenia is rather obscure in itself. There is some question that the blood vessel lining is involved in the basic idiopathic thrombocytopenic purpura process. I know of no evidence that steroids help von Willebrand's disease, and I don't know of any studies.

QUESTION: Does inhibitor to Factor VIII develop when treating hemophiliacs with cryoprecipitate?

DR. PERKINS: This can occur in any hemophiliac treated with commercial concentrate, plasma, or cryoprecipitate. There is always the risk of a factor developing which is presumed to be an antibody, which (if potent) will destroy transfused AHF as fast as it goes in. When such an inhibitor de-

velops, transfusion therapy with AHF in any form is usually useless. Such an inhibitor develops in approximately 5.0 percent of hemophiliacs. If elective operation of any kind is planned for a hemophiliac, *in vitro* tests must be run for a circulating anticoagulant against AHF.

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PARENTS' "GUILT" ABOUT CHRONIC ILLNESS

"Personally, I've never seen any parents who didn't have guilt feelings because of the chronic illness, [deformity,] or invariably fatal illness of their child. We assume that they have them. We don't speak to them of guilt feelings; but we sit down and among other things, we say, 'Well, I want to be sure that you're not thinking that something you did or didn't do contributed to this situation.' Sometimes you can just see them heave a sigh of relief. . . . It is amazing how gratified parents are for this open approach and how obviously relieved they are for the absolution of their presumed sin."

—JAMES G. HUGHES, M.D., Memphis
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Rehabilitation

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GOVERNMENT, AS IT relates to the delivery of health care services, has had as much influence in the field of human rehabilitation as in acute care, the prime reason being the economic factors inherent in human disability.

The cost of rehabilitation services, accompanied by the simultaneous loss of the disabled person's earning power, puts these services beyond the resources of most persons.

The lack of personal resources to purchase rehabilitation services from the private sector of health care has resulted in a slack demand for such services. Hence rehabilitation personnel and rehabilitation facilities have not been developed in the private sector. This brought the government into the field to stimulate development and partially to fill the need.

This article will attempt to cite the relations between government and medicine in rehabilitation by describing rehabilitation, its needs, the economic forces involved and the impact government has had on the efforts to provide it.

What is Rehabilitation?

In its broadest sense, the term *rehabilitation*—"to restore to its former state,"—could be applied to a wide range of problems from health to social to industrial. As applied to the health field, it could be used to mean restoration of health when health has been lost. This would encompass nearly the whole of health care. However, common usage has implied the limitation of meaning primarily to

the area of evident physical disability which is of long duration or at least potentially so, resulting in a significant loss of function by the individual involved. Examples are trunk or extremity paralysis or damage or loss, so as to interfere significantly with self-care, mobility or job performance. Disability of any of the major organ systems will likewise interfere with a person's ability to function—for example, pulmonary or cardiac disability, loss of sight, hearing, or speech. Usage has also included vocational training or retraining and employment assistance as a part of the rehabilitation process.

Place in Medical Care

Rusk¹ has called rehabilitation the third phase of medical care. The logic of this requires labeling the other two phases as prevention and therapy. It also implies that rehabilitation is something other than therapeutic. It certainly is a definitive form of therapy and could, therefore, be labeled therapeutic; however, because medical education and the delivery of medical services have focussed primarily on the acute and episodic aspects of disease and disability, the health services have not provided significant restorative resources to those persons with residual incapacitating disabilities. The use of the concept or label of rehabilitation as the third phase of medicine is more to highlight the need to develop rehabilitation resources and to provide rehabilitation service than to imply that it is not a part of definitive therapy.

Historical Background

Historically, the patient's personal physician provided for the total spectrum of his health care

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needs, including rehabilitation, to the best of his ability. It was not identified as any particular phase of medical care; the physician did not have specialists, special allied health personnel, special devices or facilities, or agencies to refer the patient to. The total health service available to the patient was supplied by his physician to the best of that physician's knowledge and skills and by the health facilities and staffs available to that physician. As medical knowledge and new techniques multiplied at an unparalleled and ever-increasing rate, several things happened to decrease the personal physician's ability to provide all the health care needs of his patients. Specialization and subspecialization into narrower limits and fields occurred. New classes of allied health personnel began to appear, such as physical and occupational therapists, clinical psychologists, and vocational and employment counselors. The physician was neither trained nor experienced in the use of these allied health persons. Hence, he could not appreciate their services nor find the means to use them. They did not become a significant part of his therapeutic regimen in caring for his patients with residual and severe disabilities.

Hospital facilities simultaneously became better organized to provide intensified care for acute and episodic illnesses. The average length of stay decreased to approximately one week. Fast turnover was encouraged to improve efficiency and to reduce the cost of hospitalization. The delivery of health care became focused on the physician's office and the community hospital where he had staff privileges. The acute and episodic illnesses received excellent service; however, patients whose illness left them with an incapacitating disability found few opportunities for restorative care. Their physician was neither skilled nor experienced in providing rehabilitation services nor in using rehabilitation personnel to assist him. The hospital was not prepared to serve a patient needing six or more weeks of intensified care and did not have the rehabilitation facilities for restorative procedures. For the patient unable to take care of himself or to return to his former job, one of several alternatives occurred: He stayed unduly long in the acute hospital at great cost and little therapeutic benefit, he went home where family or friends took care of his daily needs, or he went to a chronic disease facility or nursing home for maintenance care for an indefinite period.

At this point of the historical background, it

should be noted that these alternatives were not necessarily bad nor inappropriate for many of the patients. Experience to date and in retrospect reveals that somewhere between 25 and 35 percent of the patients severely disabled would benefit significantly from rehabilitation. This means that the remainder would not benefit, that we do not as yet have appropriate therapeutic means, and that maintenance care is all we have to offer. But the number that would benefit is significant and highlights the tragedy which results when disabled persons are unnecessarily set aside from a functional and productive life.

Historically there are essentially two identifiable situations which, working in parallel, brought the concept of rehabilitation to the health profession, to the public and to those involved in the organizational concepts of the delivery of health care services.

During World War II, the armed services became acutely aware that the policy of military personnel being either on full duty or in a hospital did not properly recognize the existence of an in-between convalescent group. They jammed the hospital facilities inappropriately and did not receive restorative services designed to return them to full duty. Rusk¹ recognized the problem within the Air Force medical facilities. He was able to organize and develop rehabilitation and convalescent facilities and programs which provided appropriate restorative care to these military personnel. The lesson and examples were not forgotten when the war ended. Dr. Rusk became a leading spokesman and developer of rehabilitation programs in civilian educational and health facilities with his base established at the New York Institute for Rehabilitation Medicine in New York City where it was affiliated with New York University.

At this same time, epidemics of poliomyelitis began increasing in frequency and severity in this country. Improved acute care lowered the mortality rate but left large numbers of children and young adults with severe residual paralytic disabilities. Landauer,² a pediatrician and rehabilitation expert who was assistant medical director for the National Foundation for Infantile Paralysis, established a series of regional respiratory and rehabilitation centers to provide expert and advanced rehabilitation services. The National Foundation also became the prime stimulator and financial supporter of training and development of the physical and occupational therapists, as well as other

professional members of the rehabilitation team.

The health profession and organizations dealing with these two situations became the key developers and organizers of rehabilitation concepts, programs and facilities as we know them today.

Reasons for Government Action

Economic Aspect

Incapacitating disabilities have a profound economic effect upon the individual and his family. They create unusually high medical costs because of the intensity and long duration of medical care required. They simultaneously destroy the person's ability to create income. Very few persons have sufficient resources to meet this double economic force. The daily hospital cost of rehabilitation services is equal to that of acute hospital care but is much longer; therefore, the total cost is greater. The average acute illness hospitalization period is around one week, whereas the average rehabilitation hospitalization program is six weeks or more, some running to six months or more. Health insurance coverage for rehabilitation services has been very spotty and essentially negligible (until quite recently when changes in contracts have begun to provide benefits for rehabilitation care). The net result has been the inability of patients to pay for rehabilitation service, which in turn meant they could not go to a private hospital; therefore, the private hospitals did not have the demand to develop or provide such service, leaving the government the only significant resource.

Government Effect on Rehabilitation

The effect of government on rehabilitation has come from all three levels—federal, state, and local. The federal government provided funds for development of programs, for support of services, for construction of facilities, for training of manpower, and for research. State government provided payment for services and established standards, and local government provided mainly services. These three levels of effect will be described in detail.

Vocational Rehabilitation

The vocational rehabilitation program for civilians was established on a national scale in 1920 under the jurisdiction of the Vocational Rehabilitation Administration. It involved the provision of rather limited services by designated state agencies,

operating with federal help, to adjust physically disabled persons to work. Medical and restorative services were introduced for the first time by federal legislation in 1943, which provided federal financial participation in meeting their costs. The same law also widened the scope of the rehabilitation effort by making mental disabilities a basis for services.

In 1954 Public Law 565 gave the program new impetus by enlarging incentives to reach toward new goals. Federal grants to states for support of basic rehabilitation activities increased from \$24,000,000 in 1955 to \$71,000,000 in 1963, and the amounts appropriated for state legislatures for their basic rehabilitation services tripled in the aggregate. Significantly, the 1954 legislation added research and training activities to the program.

Simultaneous with the impact of government on services by the reimbursement technique was the provision of construction funds. Funds for construction of in-patient rehabilitation facilities have been primarily from two sources: (1) community fund raising, and (2) government, including federal, state and local. The government source has clearly predominated. The mechanism has been through the 1954 amendments to the Hospital Reconstruction Act (Hill-Burton or Hill-Harris). This provided appropriations on a matching basis of approximately one-third each from the federal and state governments and one-third from local sources, either private or governmental. It further stated that a certain portion of the total funds allocated to the state (based on population criteria) were to be for rehabilitation facilities. To my knowledge, there have been few if any rehabilitation facilities built in California within the past 20 years which did not obtain the major portion of their funds from tax sources. It should be noted here that reference is made only to those facilities which are or could be certified by the state under the criteria established and previously mentioned. There are facilities—principally convalescent, extended care or nursing homes—which may incorporate the term *Rehabilitation* into their names or as listed services but which do not provide services of the type or quality which would qualify for certification.

The few rehabilitation facilities which are out-patient only have not been included in this discussion because most rehabilitation facilities offer both in-patient and out-patient services.

Since those amendment changes occurred and

up to the present date, there has been a total of \$8,500,000 from the state and \$8,900,000 from the federal government allocated for rehabilitation facility construction in California. These funds went to a total of 25 rehabilitation facilities, of which 18 were private and six were public. These 25 facilities represented a total of 340 beds with 144 private and 196 public. The distribution of funds was 75 percent to the private and 25 percent to the public sectors. Comparing the dollar distribution with facility and bed distribution between public and private would appear to create questions of cost usage. However, the figures are misleading in this sense because the type of facility and program, rather than numbers of beds, determines cost. For example, bed numbers bear little relationship to size of ambulatory facilities attached or free standing.

Another point should be noted when using these figures: There is no universally accepted definition of rehabilitation and no such licensing category, only the certification procedure to be mentioned later. A rehabilitation facility might have 100 rehabilitation beds but request certification of only 50 for purposes of reimbursement. A facility might apply for Hill-Burton funds under the "long-term" category even though it is being designed and intended for rehabilitation purposes. It is well known that a number of such instances, representing several hundred beds, have occurred in California. The only problem this creates is a greater investment of local funds beyond the required matching amount because of the greater construction costs inherent in rehabilitation facilities as compared with "long-term" facilities. These points are merely to emphasize the fact that any published figures on the number of rehabilitation beds in the state and data on federal and state allocations for construction of these beds are less than actuality.

In addition to the impetus in rehabilitation construction by the government, the Hill-Burton allocation procedure set up construction criteria for rehabilitation facilities which served to insure design of facilities capable of providing a high level of comprehensive rehabilitation service. For a construction application to qualify, there were certain minimal services required, such as medical, social, psychological, and vocational. Formulas for minimal square feet per bed and for physical and occupational therapy treatment areas, as well as many other functional details, were also required. By these mechanisms, reasonably high standards of de-

sign and planned functional programs were established to the benefit of the patient who would be receiving service in these facilities.

The application and appropriation procedure also included geographic area priority determinations which served to prevent duplication and to assist in establishment of facilities in areas of need.

Government as a Rehabilitation Service Resource

Initially the government provided rehabilitation services through public hospitals. In California this meant the county and veterans hospitals. These sources were considerably ahead of most governmental units in the country, with the exception of New York and a handful of local units in other states. These county rehabilitation facilities evolved after World War II, gradually emerging during the 50's. If we consider these county and Veterans Administration rehabilitation facilities as the first major impact of government on rehabilitation services in California, then the next or second major impact occurred in 1961. The state government, through the Public Assistance Medical Care Program (PAMC), developed a means of paying for rehabilitation services to recipients of Old Age Security and to persons designated as totally disabled (ATD) who were in need of such services. This involved the reimbursement of cost for rehabilitation services provided by a rehabilitation facility recognized by the state as being competent to render adequate rehabilitation service. Recognition of these facilities involved joint and cooperative action by the state departments of Public Health and Social Welfare in developing definitions, criteria and standards for rehabilitation facilities, services and personnel that would have to be met as a requisite to certification of a rehabilitation facility. Eligibility for reimbursement for services required this certification. These standards in themselves represented a significant impact of government on medicine, for establishing them was one of the few instances in which government (up to that time) had evolved standards involving quality of health service and personnel, rather than facility licensing alone.

The effect of government reimbursement for rehabilitation services in a certified facility, whether public or private, took several forms. The published criteria for certification established relatively high standards for rehabilitation facilities and, in fact, became the first such standards available.

TABLE 1.—*Rehabilitation Bed and Facility Growth in California*

	<i>Rehabilitation Facilities</i>			<i>Rehabilitation Beds</i>		
	<i>Total Number</i>	<i>Private</i>	<i>Public</i>	<i>Total Number</i>	<i>Private</i>	<i>Public</i>
1960	13	6 (46%)	7 (54%)	320	100 (31%)	220 (69%)
1962	17	8 (47%)	9 (53%)	490	164 (33%)	326 (67%)
1968	37	18 (49%)	19 (51%)	1839	542 (30%)	1297 (70%)

This raised the quality of services in borderline facilities which attained certification and established an adequate baseline level of quality. Another effect was the stimulus to increase the availability of service by increasing the number of facilities, number of beds and the number of trained rehabilitation personnel in all fields.

The third major effect that government participation had on services occurred in 1966 when Medicare and Medi-Cal became effective. Benefits under these plans included reimbursement for rehabilitation services. This replaced the PAMC coverage and extended it to many more persons. The standards for participation were quite similar to those that had been established by the state under PAMC.

As the state and federal governments developed means for reimbursement for rehabilitation services, so did the health insurance industry. Although the industry has been much slower than the government and has been much more restrictive in its willingness to reimburse for rehabilitation service, nevertheless it has been moving. It would appear to be fair to say that the initiative of government in this field has had an influence upon the health insurance industry to the benefit of the patient needing rehabilitation services, whether he receives it in public or private facilities.

Evidence of the effect that state reimbursement (first under PAMC and then through extension through Medicare and Medi-Cal, along with the Hospital Reconstruction Act amendments of 1954) can be seen in Table 1. The table shows the number of rehabilitation facilities and beds distributed between public and private facilities which meet the criteria of certification referred to above. The numbers are compared, using three definable time points of government impact; namely, the 1960 (pre-PAMC coverage), 1962 (PAMC coverage), and 1968 (Medicare and Medi-Cal coverage). The number of rehabilitation facilities has almost tripled in the state, from 13 to 37. The number of beds has increased almost six fold, from 320 to 1,839. It is interesting to note that the distribution between numbers of public and private facilities

(approximately 50-50) and numbers of beds (approximately 3:1) has not changed significantly. Only the numbers have increased, and on an equally proportional basis.

Rehabilitation Manpower

Physicians

As was mentioned earlier, in discussion of the historical background of rehabilitation, the patient's personal physician was the prime source of rehabilitative care, even though it was not identified as such but merely considered a part of his medical care process. The family physician and various specialties, such as the orthopedist, pediatrician, surgeon and internist provided medical restorative services to the disabled as a part of their routine. However, as the rehabilitation concept began to emerge as a special phase of medical care, specialty emphasis was given to it.

One of the results was the development of the specialty of Physical Medicine and Rehabilitation. This emerged from the specialty of physical medicine where the physicians dealt primarily with physical means of therapy such as diathermy, heat and cold, massage and the like. At first the practitioners of this specialty focussed mainly on neuromuscular disorders and non-surgical orthopedics. They knew how to make use of physical and occupational therapists and other allied health professionals who function in the rehabilitation setting. As they became experts in the field, they enlarged the scope of disabilities they dealt with, adding cardiac, pulmonary, neurologic, and pediatric disabilities—in fact, any disability to which the process of rehabilitation could be applied.

This created the potential for specialty jurisdictional disputes in certain instances, which is typical of any emerging specialty. Historically such disputes gradually diminish or disappear as the specialty establishes its base, its area of competence and the need for its services. It would appear that we have now reached this point with regard to rehabilitation. In addition, it is encouraging to note that the other specialties are rapidly becoming

aware of the need to provide rehabilitation services to their patients and are recognizing that they have special skills within their specialty to bring to the process. This broadening of specialty interest is a major advance in rehabilitation service.

Allied Health Personnel

The use of allied health personnel is probably more advanced in the rehabilitation effort than in most areas of medical practice. Nursing is well along the path of producing rehabilitation nursing specialists, with skills in bowel and bladder training and the teaching of daily personal maintenance. Physical and occupational therapists provide the basic techniques in muscle strengthening, ambulation, weight transfer, activities of daily living, and extremity dexterity and function. They train patients in the use of mechanical assistive devices which substitute for hand and finger function, as well as other extremity functions.

The clinical psychologists are able to determine the presence and extent of brain and intellectual damage and residual functions. They measure and analyze the emotional reactions of the patients to their disabilities and environment and help carry them through periods of depression and back into a motivational phase. The medical social worker determines the extent of social and economic impact upon the patient and his family and mobilizes resources to carry them through the economic crisis common to these severe and prolonged periods of great expense and loss of earning power. The orthotist and prosthetist design, develop and produce mechanical assistive devices for the various lost extremity functions. These devices range from splints and braces to externally powered prosthesis which can nearly replace total extremity activity, including hand function. The vocational counselor tests remaining functional skills and assists in establishing new job goals and training to achieve them.

Putting all of these allied health professionals together into a common effort under the direction of the physician to assist the patient to recover some or all of his lost functions becomes a major team effort. The use of the concept and term "team" has been greatly overworked, almost to the point of cliché. Yet it remains a group effort for best results. These allied health professionals become much more skilled in the application of their techniques than the physician directing them. They stretch his availability and produce better results. The physician's part here is that of final

authority in determining the ultimate objective and goal, the physiological limits of the patient, and the priority of the various parts of the program to achieve the patient's rehabilitation goal in the shortest possible time within the safety limits of that individual.

Funds for training these personnel have come mainly from the federal government through the Department of Social and Rehabilitation Services (formerly known as the Vocational Rehabilitation Administration) under the direction of Miss Mary Switzer. Some of these funds come directly from the federal agency to the recipient through the competitive grant mechanism, and others come through the California State Department of Rehabilitation where state matching funds are added. This agency has been the prime stimulant for the development of medical school departments of physical medicine and rehabilitation by providing developmental and support grants for creation, expansion, and maintenance of these departments. In 1963, sixty-one medical schools received financial support for undergraduate training in rehabilitation medicine. They have provided training fellowships to produce specialists and funds to provide for teaching of rehabilitation in medical curricula. In fact, in 1963, this agency (SRS) spent \$13,000,000 in training rehabilitation personnel of all categories.

Research

Efforts to improve our knowledge of problems related to disability and to develop devices and techniques for restoration of function have been made by the support of research in rehabilitation. The prime mover in this area has been the Social and Rehabilitation Services Administration. As previously mentioned, federal legislation in 1954 added research activities to the responsibilities of this agency. An example of growth in research funds for rehabilitation is to note that from the small start in 1954 in accord with legislation, the agency spent \$10,500,000 on research in 1963.

Not all the credit for support of research in this field can be given to the federal government or even to one agency, although it has certainly been the dominant force. Other agencies of the government have been involved, such as the National Institutes of Health and its parent agency, the U.S. Public Health Service. Voluntary health organizations have had a very active role in research and development in rehabilitation, such as the National

Foundation, the Heart Associations, and the Arthritis Foundation, among many. In fact, these organizations were actively engaged in support of research and development in the field of rehabilitation before the government.

Research and Training Centers

In 1961 federal legislation authorized the establishment of Rehabilitation Research and Training Centers based at universities and located on a regional basis. To date, 20 such centers have been established. Four categories of such centers have emerged; they deal with medical problems, vocational, mental retardation, and deafness. One of these is in California, a Medical Research and Training Center located at the University of Southern California School of Medicine. In addition to these centers and in a different funding category is a Spinal Cord Injury Center funded in part by the Social and Rehabilitation Services Administration, which is located at Rancho Los Amigos Hospital in Downey, California. This center is regional in nature, serving California, Nevada and Arizona.

Application to Welfare Concepts

An interesting and potentially significant event occurred in the federal government a little over a year ago which bears some relationship to this subject of government and medicine.

All concerned with the problem are fully cognizant of the increasing generalized concern over the growth of welfare costs, programs, and philosophy. The Johnson Administration sensed this and struggled with it. Evidence of such concern appeared during the reorganization of the Department of Health, Education, and Welfare under the leadership of the then Secretary, John Gardner. The Welfare Agency was placed under Miss Mary Switzer, who was then the Commissioner of the Office of Vocational Rehabilitation. This reorganization resulted in the new agency named Social and Rehabilitation Services. Medicaid, as a welfare function, was placed in the SRS agency. But the most significant part of this event was the philosophy expressed in the reorganization—namely, to

apply the concepts of rehabilitation to welfare. This means to shift the emphasis from “dole” to “restoration.” The implementation will be difficult and cumbersome, and it will require a long time. It may not succeed. But, the intent is encouraging and the ramifications are of great magnitude.

In conclusion, this is a summary of government's influence on rehabilitation:

- Provision of rehabilitation services in public hospitals.
- Payment for rehabilitation services in qualified rehabilitation facilities.
- Establishment of standards for certification of rehabilitation facilities.
- Construction funds for rehabilitation facilities.
- Establishment of regional rehabilitation centers.
- Educational funds for development of rehabilitation manpower, including physicians, nurses, and a broad spectrum of allied health personnel.
- Stimulation and support of research in the field.
- Application of the rehabilitation concept and approach to welfare.
- Establishment of vocational training facilities, programs, and payment for services.

This listing is incomplete and sketchy. Yet, it provides a good look at the effect that government, at all levels, has had on medicine in the field of rehabilitation. In dollars spent, numbers of facilities and beds constructed, and volume of research, the impact is certainly less than in other areas of medicine. However, taking into account the size of rehabilitation services in relation to medical services as a whole, it can be seen that the government's push in this area has been specialized and unique and has had a proportionately greater impact than the public or those in the health professions have generally been aware of.

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Medical Schools of California

UCLA School of Medicine

An Historical Vignette

THE GENESIS AND EARLY history of UCLA School of Medicine has been set forth in two earlier papers. The first of these was a brief sketch in 1964,¹ the second a much more complete account in 1966.² Accordingly the present account will focus primarily on the school's history from the time it began its abode in its first permanent buildings in 1954.

Substantive administrative actions leading to organization of the school include, (1) Board of Regents' approval of Regent Edward A. Dickson's motion to establish a medical school as a component of the University of California, Los Angeles (UCLA), 19 October 1945; (2) appointment by President Robert G. Sproul of a faculty advisory committee to plan the early development of the school, including selection of a location and recommendation of nominees for the post of dean; (3) passage of the initial appropriation bill to fund the school, 5 February 1946; and (4) appointment of Dr. Stafford L. Warren as the first dean in 1947.^{1,2} The first four departmental chairmen, Drs. J. S. Lawrence (Medicine), C. M. Carpenter (Infectious Diseases), A. H. Dowdy (Radiology) and W. P. Longmire, Jr. (Surgery) and Miss Louise Darling as librarian, were appointed in 1947. Pending completion of permanent buildings, faculty and staff were housed in temporary quarters on the UCLA campus.^{1,2}

UCLA School of Medicine admitted its first class (28 students) in 1951. When that class graduated in 1955, the year 1951 was designated by the Council on Medical Education and Hospitals as the official organization date of the school, in line with the council's requirement that an initial four-year program be completed before full approval is granted (cf. 3, p. 565). Thus, with an official organization date of 1951, the UCLA school became the 81st approved medical school in the United States.³

There have been three fairly distinct phases of construction of permanent buildings for UCLA School of Medicine. The first began in 1951 and ended when the Medical School building and the University Hospital were occupied in 1954 and 1955 respectively. (The hospital, opened in part in 1955, was not ready for full use in the teaching program until 1956 — hospitals, like Kipling's ship, need time to "find themselves," to become effective integrated patient care and teaching units.) Clinical teaching programs had previously been located in selected public and private hospitals.^{1,2} One of these, Harbor General Hospital, has become associated by contract with UCLA's medical teaching programs, while the Los Angeles Veterans Administration Center continues a close affiliation.

The second phase of building began to take form shortly after the first phase ended. It included addition of four new units to the original complex. These were the Brain Research Institute (founded and planned under the leadership of Professor

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H. W. Magoun), the Neuropsychiatric Institute, the Laboratory of Nuclear Medicine and Radiation Biology and the Marion Davies Children's Clinic. All were completed by 1962.

The third and largest building phase was planned during the second phase—indeed, hammer and saw have never really been quiet since 1951, although one hopes this may happen as the third phase is now drawing to a close. It has been notable for expansion and coordinated remodeling of the original medical school and hospital as well as addition of such major new components and facilities as the Jules Stein Eye Institute, the Clarence and Margaret Reed Neurological Institute, the Hazel Wilson Pavilion, the Gwynne Hazen Cherry Laboratories, and the Rehabilitation and Mental Retardation Institutes. In this period two new health science schools, the Schools of Dentistry and Public Health, were added to the Center for the Health Sciences. These were so located that the whole organization of health sciences schools and facilities is clustered around the all-important Biomedical Library, now the major resource for biomedical literature in Southern California.

Salient information on each unit of the health sciences complex (to 1967), including date completed, size and construction materials, cost, financing and commentary is provided in the section on "Los Angeles Buildings and Landmarks" in the *Centennial Record* of the University of California (4, pp. 335-343). Brief histories of the Schools of Medicine, Dentistry, Public Health and Nursing, and of Medical School departments are also set forth in the Los Angeles Section of the *Record*.⁴

UCLA School of Medicine and the other eight American medical schools organized between 1943 and 1956 chose their dates of birth⁵ wisely. For these schools the period of early growth and development came close to the beginning of federal support of medical research and training related to research and of matching grants for research construction under the aegis of the National Institute of Health (NIH). From 1947 to 1966 the dollar support for medical research in the United States increased 24-fold. The proportion of this support provided by NIH, significant from the start, rose continuously. This remarkable socioeconomic development has been well described by J. A. Shannon, one of its chief architects.⁶ Its pervasive effect on American medical education was recently analyzed by T. B. Turner.⁷ Direct federal assistance for general support of medical education was

initiated by the Health Professions Educational Assistance Act of 1963, somewhat expanded and liberalized by amendments in 1965.⁸ Without these programs of federal aid the nation would lack the existing strong educational programs in medicine so crucial in meeting the looming doctor shortage.

The first undergraduate medical curriculum at UCLA conformed with the general pattern of American medical curricula, which, as to courses and their sequence, changed little from 1920 to the 1950s. While revision and development of curricular microstructure were continuous in all medical schools in the United States during this period, it became more and more clear that the "information explosion" which stemmed from the accelerating pace of discoveries in biomedical research that marked the post-war era could not be contained by such methods. Little by little the curriculum had become overloaded and beset with makeshift modifications which virtually eliminated options and free time. By the 1960s it became clear that the curricular pattern that had worked so well for so long had become unsatisfactory. Curricular reform, which had tenuous beginnings before the war, now became recognized as necessary.

The first major revision of the medical curriculum at UCLA was designed in 1964-5 and adopted in 1966. This new curriculum, like many others, comprised a common core of basic science and clinical training, substantial blocks of elective time and considerable increase in free time. The elective programs and free time provided for flexibility and diversity. These features permit the student, in part at least, to mold his medical education to his abilities, interests and goals. They also provide a built-in device for continuous adaptation to the rising pace of change in medical science and clinical practice. The new curriculum pattern was planned in recognition of the fact that medical students no longer face a common future career. Only in its very core is medicine a single profession today. Outside that core lies a host of different careers, varying from public health and hospital administration to biochemical research, from gynecologic endocrinology to cardiac surgery, from academic medicine to family practice.

This brief account may be ended with a few comparisons which highlight the remarkable growth and development of UCLA School of Medicine in less than two decades. In the academic year 1951-52, the total student enrollment

was 28 (a first year class); in 1968-69 the total was 1,297. This figure includes 391 undergraduate medical students, 709 interns and residents and 197 M.S. and Ph.D. candidates. In 1951-52, the regular faculty numbered 34; in 1968-69 that figure was 248. A year ago a steady state was projected for 1972-73, in which the undergraduate medical students would total 512, interns and residents 913 and M.S. and Ph.D. candidates 300 for a student body of 1,725. Those assumptions may well prove an underestimate and do not include many hundreds of students in fields related to medicine in whose education the faculty of the School of Medicine participates significantly.

JOHN FIELD, PH.D., Associate Dean

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The Patient: A Statistic or a Person

ROGER O. EGEBERG, M.D., *Los Angeles*

WHEN THE TILLERS in the field of public health approached what they thought was the point of diminishing returns in the cleansing of the environment, they turned their attention to the prevention of illness in a more personal way. They began to educate people in schools and elsewhere on matters of personal hygiene, diet, and on keeping healthy. They threw themselves into the job of influencing the epidemiology of some of the worst contagious diseases, such as tuberculosis and the venereal diseases, broke into the practice of medicine to treat venereal disease and tuberculosis, and then showed concern over the prenatal period of women in the slums. Gradually, they even took on a bit of curative medicine here and there.

Through all of these advances, their knuckles were continually rapped by the doctors in practice who looked upon each advance as an infringement on what might be considered the practicing physician's province. What the public health profession wanted was a broader opportunity to practice preventive medicine — environmental, educational, and personal. The workers in public health and preventive medicine have accomplished their environmental tasks, fighting air and water pollution with a fair degree of vigor. They have increased their efforts in public education, but would seem to have lost this battle to the schools. They have continued their efforts in personal disease prevention through well-baby clinics and prenatal clinics, and they have treated the social diseases that are violent threats to community health. Further they have continued their watch on the epidemiology of contagious diseases, their search for tuberculosis

spreaders, their epidemic warnings, and so forth. And now, with broad new laws from Congress, they find themselves in the center of planning for comprehensive health care, the integration of all the forces having to do with the health of the population: Control of the environment, education, prevention, and treatment. Are they ready for this job?

I don't think so.

Let us look at the practitioners of medicine. Through 20-25 centuries they have followed the ethics of Hippocrates and retained rather stubbornly the blinders that kept them from looking at medical problems population wide. They have looked at the problems of health as individual ones, following the precept that if the doctors take care of the immediate needs of their patients all is well in the health world. They have fought with vigor the encroachments of the legions of public health. They have ignored with amazing success the ills of large segments of our population, and half of them would seem to deny to this day that medicine is progressing fast enough to require their continuing education beyond medical school and early training.

Are these people ready to lead us in the newer approaches to health care?

Obviously not.

What lies ahead of us? Many, many millions of patients for whom health care will have to be organized, for whom physicians and allied health workers must be secured, for whom broad plans must be made and for whom many, many organizations must be administered. This lies ahead. The best laid plans, no matter what we call them, will be without meaning if we cannot get the people to carry them out, and certainly hosts of medical personnel, even if we had them willing to work, could not get very far without a plan.

Are we looking for a new breed in this very broad field amply divided into disciplines, subdis-

The author is Assistant Secretary, Health and Scientific Affairs, Department of Health, Education, and Welfare. At the time he submitted this communication he was Dean of the School of Medicine, University of Southern California, and formerly was chairman of the California State Board of Public Health.

Presented as part of a panel "Preventive Medicine: You Ain't Seen Nothing Yet," before the section on Preventive Medicine and Public Health at the 98th Annual Session of the California Medical Association, Los Angeles, March 15 to 19, 1969.

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ciplines, and sub-subdisciplines? I hope not, but certainly the practitioners of medicine and the workers in the broad discipline of preventive medicine and public health are going to have to learn something from each other. I would hazard the guess that you in the field of public health may have less to learn and are certainly much more aware of the broad problems than the practitioners. How can this best be measured? Perhaps by a better look at the patient, that person whom we want to make well and keep well, that person who must react to us if we are to begin to accomplish our overall mission.

Obviously, there is much that can be improved in the medical care of the rich and the middle class. That will be worked out not without idealogic clashes, and it will be worked out in the course of the next decade or so. But the poor and the problem of their care is upon us. The care of 20 or 30 million people who have had little or no care heretofore—for them the era of “come and get it” medical care made only a meager impact on their total numbers and “come and get it” will not be the principle through which you will reach them. They don’t know what medical care or health care really is.

They must be taught what medical care can mean to them and they cannot be ordered to come and listen. For a generation or more, if we are to reach them and perhaps from now on, the delivery of the care will have to be tailored to their pattern of life instead of to our middle class concept of what’s good for them.

In spite of the talk about the mainstream of medical care I can’t believe that our government will long continue to participate in a program of

remuneration which leaves the amount up to the honor of the purveyors. Small groups can have honor, but when it comes to large groups so many factors enter into the picture from dire need to the matter of taste, love of people or resentment of them, service, interest, opportunism, aggressiveness and lack thereof, that the scope of what might be called integrity becomes unmanageably broad. If this is so and if the government will indeed suggest set fees and, in certain instances, salaries, as a means of remuneration, one has a problem of incentive to be worked out—incentive to do good work, incentive to do it humanely, with a warm relationship, and with efficiency and dispatch. The blindness of those who think that because they take good care of *their* patients *all* people have good care is matched by the blindness of those who would arrange for poor people (without means of transportation) to visit clinics for tuberculosis on one day, prenatal care on another, well babies on a third, and so forth.

If you will take a thoughtful and humble look at yourselves and your patterns, if you will sense the importance of the personal factors in the health care of people, if you will evolve ways of attracting the poor to you, and if you will maintain or develop an amazing degree of flexibility, of open mindedness with respect to the methods you may use, if you will have among you a number of people inspired by the importance and the scope of this challenge, then you in public health may well be the ones to fit the bill. But you will never fit that bill if your focus is not heavily upon the human being who will be the recipient of these services and ministrations. Take a good look at him; in so doing, you will shape your future.

THE TILT TEST FOR SHOCK IN UPPER GASTROINTESTINAL BLEEDING

“If there’s a question about shock or impending shock in patients with massive upper gastrointestinal hemorrhage, the tilt test is a good one—namely, the head of the patient’s bed can be elevated 30 to 60 degrees and the patient can be observed for about three minutes. If he exhibits signs of restlessness, pallor, sweating, or if his pulse goes up and his blood pressure goes down significantly, shock is probably impending; and the fluid therapy has not been vigorous enough.”

—DOUGLAS A. FARMER, M.D., New Haven
Extracted from *Audio-Digest Surgery*, Vol. 16,
No. 1, in the Audio-Digest Foundation’s subscription series of tape-recorded programs.

Physician Opinions About Continuing Education Programs

Highlights of Findings in Part II of a Survey in California

*A Socio-Economic Report of the Bureau of Research
and Planning, California Medical Association*

THE SECOND REPORT of findings of the Questionnaire Survey of Continuing Medical Education, conducted under a Regional Medical Programs grant,* contains further analyses of data provided by 2,600 California physicians who completed questionnaires in the latter part of 1967. A Socio-Economic Report summarizing the first findings of the study (Vol. VIII, No. 7, June 1968) provided the initial analyses of data for most questions contained in the survey form, along with details concerning the methodology employed in conducting the study. Analysis of data contained in the Part I report suggested possibilities of further relationships among the answers to various questions, as well as additional relationships pertaining to characteristics of respondents. Furthermore, a full analysis of results required the correlation of responses to several questions with individual medical specialties, which was not done in earlier tabulations. Finally, information concerning three of the nine questions contained in the survey form had not been tabulated for inclusion in Part I.

The first article, *A Survey of Continuing Medical Education for Physicians, Selected Findings Based on 2,600 Responses to Questionnaires*, appeared in CALIFORNIA MEDICINE, 109:245-251, Sept. 1968.

*This study of continuing medical education conducted by the Bureau of Research and Planning on behalf of the Committee on Continuing Education under the auspices of the California Medical Education and Research Foundation, is being funded through a grant from the National Institutes of Health to the California Committee on Regional Medical Programs. Copies of the complete Part II report are available in limited quantities; address requests to the Division of Socio-Economics and Research, California Medical Association, 693 Sutter Street, San Francisco 94102.

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These three aspects of the data provide the content for Part II.

The significance of this portion of the findings is that they provide more specific and refined information to aid in planning programs of continuing education, based upon the perceptions of physicians in diverse specialties. Discussion in the full report clearly demonstrates the importance of utilizing modalities of continuing education to which physicians feel they can respond and which provide the most effective means of transmitting information which they can apply in their specific practices. The data suggest employing a variable approach, directed to the perceived requirements of each specialty, rather than one which is based upon the "umbrella" technique under which every specialty is covered.

Highlights of Findings*

- Physicians in rural areas are generally more satisfied with programs of continuing education than are physicians in urban areas, regardless of their specialties. Variations in levels of satisfaction also exist in different parts of the state.
- There are some marked differences in how physicians in different specialties evaluate various modalities used to transmit medical information.
- Programs presented on weekends generally appear to be more successful and easier to attend

*Includes data from the full report which may not be found in this summary.

than programs given at night; only about one physician in twelve considers it difficult to attend programs given at either of these times.

- Physicians in group medical practice are only slightly better able to attend programs than are physicians in individual practice; however, they are also somewhat less likely to find programs of interest.

- Cost prevents relatively more physicians in individual practice than in groups from attending as many programs as they would like; conversely, more respondents in group arrangements limit their attendance because of difficulties in taking time off from their practices.

- Considerable variation exists among physicians in various specialties as to how well their needs for information are being satisfied by programs currently presented. Internists, general practitioners and general surgeons appear to desire a broad range of instruction, while physicians in other specialties may require more depth in subjects relating to their own fields.

- Education need increases with number of years in practice. However, the youngest group of physicians sampled indicated a higher degree of need than did the next older group. This may suggest some gaps in the training they receive prior to entering practice.

- Respondents made a wide array of suggestions about subjects which should be given additional attention; almost half of all subjects related to disease entities, while other large blocks of answers pertained to medical specialties and to biological and preclinical sciences.

- Among specific subjects in the area of cardiovascular disease mentioned frequently were electrocardiography, anatomy of the heart, cardiac arrhythmias, employment of anticoagulant drugs, hypertension and emergency treatment of patients with cardiac arrests.

- There was sufficient repetition of specific subjects suggested by physicians in five specialties — general practice, internal medicine, obstetrics/gynecology, psychiatry and internal medicine — to warrant their suggestions being shown separately. Such suggestions can provide some further insight into program planning.

- Survey results can be used for detecting deficiencies in coverage of various subjects, as viewed by practicing physicians, which exist in specific areas of the state, and for planning programs to correct them when necessary.

Opinions About Educational Modalities According to Medical Specialty

Detailed statistics concerning evaluations of nine instructional modalities used in the field of continuing medical education have been developed from data provided by respondents. Part I presented these evaluations for grouped medical specialties. After reviewing the grouped data, it became clear that differences in the evaluation of various modalities of instruction were apt to vary according to individual specialty, rather than by the broad groupings. This was particularly true of a miscellaneous group of specialties, comprised of such disparate fields as psychiatry, anesthesiology, and pathology. Table 1 contains data about physician evaluations of modalities for 15 individual specialties, and seek to determine whether significant differences exist among them.

It also indicates mean ratings or responses by physicians in each medical specialty to each of the nine modalities listed on the questionnaire and presents a broad overview of the differences which exist.

Lastly, it provides insight into how modalities are viewed by physicians and an overview of the relative merits of all nine modalities as perceived by physicians in each individual specialty. Most details about individual modalities become immediately apparent from the table; however, a few remarks are in order about each specialty and how its member physicians view all of the modalities.

Dermatologists find textbooks and journals and two- or three-day symposia most valuable in fulfilling their needs for medical education. Grand rounds are also rated relatively high, as are bedside postgraduate courses. Medium- to long-term in-service programs, Audio-Digest tapes, and radio and television conferences rate relatively low.

Internists prefer two- or three-day symposia, rating them somewhat above the next-ranked modality of textbooks and journals. They also show a preference for grand rounds and for long-term traineeships. Both radio and televised courses are considered of marginal value.

Pediatricians rated short symposia considerably above any other modality. Reading materials were tied for second place with long-term traineeships; both modalities were followed closely on the rating scale by one- to three-week programs and grand rounds. Radio conferences were rated well below other modalities, as were televised instructions.

TABLE 1—Mean Rating* of Selected Modalities Employed to Transmit Medical Information, by Individual Specialty.
(Scale: 1 = least valuable, 4 = most valuable)

Specialty	Modality								
	2 or 3 day Symposia	Textbooks, journals, etc.	3-6 month traineeships in teaching institutions	Hospital grand rounds and clinics	Bedside postgraduate courses in medical schools	1-3 week in-service programs	Audio-digest tapes	Hospital TV conferences from medical schools	Hospital radio conferences from medical schools
Dermatology	3.2	3.3	2.3	2.9	2.7	2.4	1.7	2.2	1.4
Internal Medicine	3.4	3.1	2.7	2.8	2.5	2.3	2.4	1.9	1.5
Pediatrics	3.4	2.9	2.9	2.8	2.4	2.8	2.2	1.9	1.4
General Surgery	3.3	3.3	2.7	2.9	2.4	2.7	2.1	2.3	1.5
Obstetrics-Gynecology	3.6	3.0	1.9	2.4	2.4	2.2	2.5	2.0	1.6
Ophthalmology	3.7	3.2	2.6	2.3	2.0	2.1	2.8	1.9	1.4
Orthopedic Surgery	3.5	3.3	2.7	2.6	2.5	2.4	2.3	2.1	1.7
Otolaryngology	3.3	2.7	3.1	2.6	2.8	2.9	1.4	2.1	1.6
Urology	3.5	3.4	2.4	2.5	1.7	3.0	1.9	1.8	1.6
Other surgery	3.7	3.6	3.0	2.4	2.3	1.8	1.9	1.6	1.3
Anesthesiology	3.4	3.2	2.3	2.0	1.8	1.7	2.9	2.1	1.4
Pathology	3.7	3.3	2.7	2.3	2.2	2.4	2.5	2.0	1.6
Radiology	3.5	3.3	3.2	2.4	2.1	3.2	2.1	2.0	1.5
Psychiatry	3.3	3.1	3.2	2.4	2.5	2.7	2.1	2.2	1.6
Neurology	3.4	3.2	3.7	2.8	3.0	2.9	1.7	1.7	1.4
Other	3.9	3.3	2.4	2.4	2.5	1.9	2.3	2.6	1.8
General Practice	3.5	2.7	2.5	2.6	2.8	2.5	2.4	2.5	1.9
Total	3.5	3.0	2.7	2.6	2.5	2.5	2.3	2.2	1.6

*Means calculated excluding modalities with which respondents were not familiar.

General surgeons ranked reading and short symposia first and also gave a relatively high rating to grand rounds. Intermediate to long-term programs rated next. Television conferences rated relatively well among general surgeons; radio conferences did not.

Obstetrician-gynecologists preferred two- or three-day symposia by a substantial margin over the next highest rated modality, reading materials. Audio-Digest tapes were ranked well by physicians in this specialty. Intermediate and long-term programs and grand rounds were rated relatively low. As among other physicians, radio conferences received a low rating.

Ophthalmologists also preferred short symposia by a wide margin; however, both this modality and textbooks and journals received ratings which were, on the average, higher than the ratings given them by all physicians. Audio-Digest tapes are third in popularity, as compared with a rating of eighth among all physicians. Bedside courses, short in-service programs and grand rounds rated relatively low among physicians in this specialty.

Orthopedists appear able to find something of value in most modalities, giving ratings which are only slightly different from the ratings given by all physicians. Although short symposia are rated highest, reading materials were ranked only slightly lower. They find radio conferences somewhat more rewarding than do most physicians.

Otolaryngologists present a rating picture which is somewhat difficult to interpret. Almost as well-rated as short symposia are long-term traineeships. Also highly regarded are one- to three-week in-service programs and bedside courses in medical schools. Reading rates relatively poorly, as do Audio-Digest tapes. In general, the types of instruction most highly regarded by physicians in this specialty are those usually given in a formal manner in an academic setting.

Urologists rank reading materials almost as highly as they do short symposia. Both modalities received very high ratings. Also well-rated were one- to three-week in-service programs. Among the many modalities which these physicians consider of limited effectiveness are bedside courses, long-term traineeships, television conferences, and Audio-Digest tapes.

Other surgeons (colon and rectal surgeons, neurosurgeons, plastic surgeons, and thoracic surgeons) while probably displaying some internal differences which cannot be further refined from the available data, show some patterns in the way they rate modalities which suggest that their impressions do, in fact, differ from those of other physicians. Although short symposia and reading material are the two highest rated modalities, with the latter rated far higher than by physicians in other specialties, long-term traineeships in teaching institutions also received high ratings. Short in-

service programs were ranked relatively low by these specialists, as were both television and radio instruction.

Anesthesiologists, as most other physicians, rated short symposia at the top of the scale, followed closely by textbooks and journals. Audio-Digcst tapes received particularly high ratings—the best, in fact, among all the listed specialty groups. Ranked especially low on the value scale were bedside courses and grand rounds and clinics, as well as short in-service programs.

Pathologists rely heavily on two- or three-day symposia for continuing medical education and somewhat less on reading material. Both of these modalities, however, were rated considerably above any other. Understandably, bedside courses and grand rounds were considered somewhat less valuable by them than by physicians in other specialties.

Radiologists, as others, gave high ratings to the two most familiar modalities, two- or three-day symposia and reading materials. However, exceptionally high effectiveness ratings were also attributed to extended traineeships and to one- to three-week in-service programs.

Physicians Prefer Weekend Programs To Evening Programs

The questionnaire inquired about the level of agreement of physicians with two statements concerning ability to attend relatively short programs presented at different times. The statements were the following: (1) Courses held on weekends are relatively easy to attend, and (2) Evening programs are useful and relatively easy to attend.

Although they are not entirely comparable, since the statement concerning evening programs deals with utility as well as ease of attendance, a cross-tabulation of levels of agreement with the two statements provides some insight into physician preferences for programs presented evenings or weekends. Table 2 is a recapitulation of this cross-tabulation. Estimated totals are of all physicians in private practice and laboratory medicine in California, expanded from data supplied by 2,600 respondents to a random sample of 4,500 physicians.*

The largest single group of physicians indicated that it is relatively easy to attend programs given either evenings or weekends by checking that they

TABLE 2.—Relative Ease With Which Physicians Can Attend Programs Presented Evenings and Weekends: Estimated Total Numbers of Physicians in California.

Measures of ability to attend	Number	Percent
Little problem attending, regardless of timing	8,854	36.5
Easier to attend weekends than evenings	8,374	34.6
Easier to attend evenings than weekends	3,795	15.6
Relatively difficult any time	2,065	8.5
Indifferent, regardless of time	1,164	4.8
Total	24,252	100.0

generally agree with both statements. Over one-third of physicians (36.5 percent) fit into this group. Another third (34.6 percent) indicated a preference for weekends by showing some measure of agreement with the statement about weekends and either indifference or disagreement with the statement about evening programs. Less than half this many physicians (15.6 percent of the total) implied that they prefer programs given in the evening to those given on weekends.

The remaining 13.3 percent of physicians are divided into two groups. The larger group disagreed with both statements denoting their difficulty in attending programs regardless of whether they are given evenings or weekends. The smaller group, accounting for just 4.8 percent of all physicians, indicated indifference to both statements. Although it would be logical to assume that this group is comprised of physicians who seldom attend programs, data not included in this report indicate that this is not necessarily the case. Other responses show that this indifference does not generally imply lack of interest in programs, but may rather demonstrate frustration in taking time out from their practices.

Summarizing these data, then, the same subject should be expected to draw a higher level of attendance if it were given on a weekend than in the evening. While only about half of all physicians might find it "easy" to attend a program in the evening, slightly more than 70 percent find it "easy" on weekends.

Subjects Needing More Emphasis Vary by Geography

Table 3 enumerates general subject areas which physicians think are deserving of additional emphasis in programs of continuing medical education, according to geographic areas where they practice. This table reveals the opinions of phy-

*Data showing sample design, response rates and county groupings may be found in full report.

TABLE 3.—*Subjects Which Physicians Think Warrant Additional Emphasis in Continuing Education Programs: Estimated Percents of Physicians by Geographic Area*

Geographic area	Cancer and cancer chemotherapy	Musculoskeletal system diseases	Digestive system diseases	Respiratory diseases	Genito-urinary diseases	Endocrine gland diseases	Heart diseases	Vascular diseases	Other subjects re: Cardio-vascular system or diseases	Nervous system diseases	Nutritional diseases	Electro-cardiography	Psychiatry and Psychology	Physiology	Accidents and emergency care	Average number of suggestions per physician
Metropolitan areas:																
San Francisco Bay Area	8.9	2.0	1.5	1.3	0.1	3.9	8.4	10.8	7.4	1.2	0.5	3.9	4.9	4.7	2.6	.52
San Jose	9.9	2.8	4.2	16.9	7.0	4.2	2.8	1.4	5.6	5.6	2.8	..	.57
Sacramento	13.5	0.6	..	2.7	2.5	0.8	8.4	8.3	6.7	0.2	2.1	0.4	6.5	8.9	0.6	.63
Stockton	23.0	2.1	..	2.1	13.0	16.7	4.2	..	2.1	2.1	4.2	..	4.2	.76
Fresno	22.7	..	4.5	..	2.3	4.5	6.8	4.5	4.5	..	9.1	2.3	.75
Los Angeles-Long Beach	5.1	0.9	1.8	1.8	2.7	1.8	8.2	7.7	1.8	0.9	1.8	4.6	5.0	10.5	2.2	.94
San Diego	4.4	0.9	0.9	3.5	4.4	0.9	7.9	10.6	6.2	1.8	0.9	6.1	7.9	4.4	0.9	.87
San Bernardino-Riverside-Ontario	3.3	2.0	3.2	..	1.6	4.0	10.3	6.5	4.3	0.8	2.8	3.3	6.8	2.8	1.6	.84
Bakersfield	8.2	5.5	1.4	1.4	1.4	5.5	5.5	12.3	2.8	4.1	2.7	4.1	2.7	4.1	..	1.18
Santa Barbara	8.0	2.0	2.0	6.0	6.0	4.0	..	2.0	2.0	4.0	..	4.0	.71
Santa Ana-Garden Grove	10.0	3.3	2.2	7.8	11.1	6.7	2.2	4.4	3.3	2.2	7.8	..	.74
Vallejo-Napa	10.5	2.6	1.3	1.3	2.6	3.9	5.3	13.2	3.9	1.3	1.3	3.9	2.6	6.6	1.3	.61
Ventura-Oxnard	4.3	..	4.3	4.3	13.0	6.5	8.7	..	6.5	4.3	4.3	2.2	2.2	.68
Monterey-Salinas*56
Non-Metropolitan areas:																
North Coast	5.5	1.4	13.6	6.8	4.1	4.1	6.1	2.7	2.1	.70
North Central Coast	9.1	3.6	1.8	1.8	16.4	3.6	..	1.8	1.8	9.1	3.6	.83
South Central Coast	8.2	12.4	14.1	4.5	..	1.0	5.8	..	5.2	2.4	.87
Sacramento Valley	8.3	0.7	..	3.0	2.0	..	8.7	9.3	2.3	0.7	2.3	2.7	..	5.7	1.3	1.16
North San Joaquin Valley	11.2	4.2	3.7	0.9	2.8	1.4	11.2	9.8	2.3	0.9	..	0.9	..	2.3	0.9	.73
South San Joaquin Valley	4.6	..	1.5	6.2	7.7	4.6	7.7	..	4.6	1.5	.67
Imperial Valley†
Sierras	9.6	1.0	1.0	10.6	18.8	1.0	6.7	4.3	.66

* Insufficient response.

† Insufficient number in sample.

sicians in specific regions as to deficiencies which exist in the subject matter which they are being presented.

The table indicates 15 major subject areas which were often mentioned by physicians as warranting additional emphasis in programs of continuing education. Some decisions as to relative needs can be made by analyzing the inter-area differences in percents of physicians who suggested particular subjects. The last column in the table indicates the average total number of suggestions made by physicians in each area. These figures can serve as a general measure of need for additional continuing education programs of all types. Areas in which many suggestions were made can be assumed to be those in which many subjects are insufficiently covered, while those with few suggestions are those in which needs are being adequately met.

The need in the Bay Area relates particularly to the cardiovascular disease categories. It appears that the vascular diseases are a subject of more widespread interest than are diseases relating to the heart. Specific areas of interest not shown in the table were in the gastrointestinal system, arthritis and rheumatism, water-electrolyte balance, and endocrinology. In general, the relatively low volume of suggestions made implies a high level of satisfaction with the range of subjects covered by existing programs.

Diseases of the heart appear to be more important to physicians in the San Jose area than do diseases of the vascular system. Electrocardiography was also mentioned by an above average proportion. The two areas of nervous system diseases and psychiatry and psychology also were mentioned relatively frequently. The average total number of suggestions made was relatively low.

Physicians in Sacramento appeared to demonstrate somewhat more interest in cancer, somewhat less in cardiovascular disease. They also showed an interest in psychiatry and psychology and in physiology. Although not shown in the table, endocrinology was noted by Sacramento physicians as a subject of interest.

Stockton physicians indicated considerable interest in the subject of cancer. Almost one in four suggested that cancer should be given additional emphasis. There also appears to be a somewhat above-average amount of interest in the general subject of cardiovascular disease.

Fresno physicians demonstrated a similar pattern; however, the amount of interest in cardiovascular disease was less prevalent. The number of responses in both these geographic areas limits the reliability of these data somewhat.

Physicians in the Los Angeles-Long Beach Metropolitan Area indicated interest in a wide variety of subjects, many of which are not included in the table. Among those not included were obesity, water-electrolyte balance, psychosomatic medicine, biochemistry, geriatrics, and endocrinology. Among those subjects listed in the table, there is relatively little feeling of need for more courses about cancer and only an average amount of interest in cardiovascular disease. Nevertheless, it is estimated that approximately 1,500 physicians in the county are of the opinion that subjects relating to cardiovascular disease need more emphasis. A large number of physicians in Los Angeles are of the opinion that topics generally classified under the subject of physiology are not being covered adequately.

There is relatively little interest in additional information about cancer in San Diego. Vascular diseases appear to be somewhat more in need of attention than do diseases of the heart. Programs in electrocardiography, however, were specified by a large number of physicians in San Diego. Also frequently suggested were psychiatry and psychology, respiratory diseases, and genitourinary diseases. Although not shown in the table, physicians in San Diego suggested that angiography and pharmacology would constitute topics of particular interest.

Little pattern is shown by physicians in the San Bernardino-Riverside-Ontario area. There is virtually no interest in further instruction about cancer, and less than average interest in cardiovascular diseases. Some interest was shown in further in-

struction in the areas of psychiatry and psychology. The relatively high volume of suggestions, showing little repetition, may indicate a broad pattern of needs.

The needs of physicians in Bakersfield also appear to be varied. While showing the highest average number of suggestions in any area, the suggestions are spread among many subjects. Somewhat above-average percentages of physicians suggested additional emphasis in vascular diseases, musculoskeletal system diseases, endocrine gland diseases, and nervous system diseases. The volume of responses from this area limits the reliability of these figures; they should be used only as broad indicators of educational need.

The pattern shown in Santa Barbara reveals little. Relative to other parts of the state, the interest in additional instruction about cancer is near the average; interest in cardiovascular diseases is considerably below average. No other meaningful information is shown, based on a relatively small number of responses.

Physicians in the Anaheim-Santa Ana-Garden Grove Metropolitan Area indicated an above-average amount of interest in diverse subjects such as musculoskeletal diseases and nutritional diseases, as well as unlisted specific subjects such as rheumatism, arthritis and obesity. Just one in ten physicians in this area was of the opinion that more attention should be given to the subject of cancer. There exists considerably more interest in further information about vascular diseases than about heart diseases.

A relatively large proportion of physicians in the Vallejo-Napa Metropolitan Area showed interest in additional programs in vascular diseases; fewer were concerned about heart disease. The percent of the opinion that cancer is insufficiently covered was somewhat above average, as was the percent indicating an interest in endocrine gland diseases.

The low number of responses from physicians in the Ventura-Oxnard Metropolitan Area limits the degree to which these statistics can be used. Nevertheless, the data indicate that physicians in the area are of the opinion that further instruction concerning heart disease is warranted, whereas adequate attention is currently being devoted to both cancer and stroke.

The number of suggestions made by physicians in the Monterey-Salinas Metropolitan Area was also insufficient to warrant any conclusions. By

TABLE 4.—*Defined Subjects Related to Cardiovascular Disease: * Estimated Number of Physicians Who Specified That Subject Needs Additional Emphasis*

<i>Specific Subject</i>	<i>Number of Physicians</i>
Electrocardiography	365
Cardiology	279
Anatomy of the Heart	247
Cardiac Arrhythmias	228
Anticoagulant Drugs	162
Hypertension	148
Emergency treatment of heart patients	138
Myocardial Infarct	119
Arteriosclerosis	99
Angiography	90
Resuscitation	83
Pulmonary Heart Disease	79
Pacemakers	62
Pediatric Heart Disease	60
Heart Arrest	52
Varicose Veins	48
Embolisms	43
Hematology	41
Rheumatic Heart Disease	29
Surgical treatment of Stroke patients	29
Congenital Heart Defects	24
Heart Surgery	23

*Excludes general references to heart disease, stroke or other non-specific responses; see Table 3 for these data.

making very few suggestions, physicians in this area implied little need for additional programs.

Physicians in the north coast area indicated a higher level of interest in additional instruction in heart disease than in vascular disease. They generally feel that sufficient information about cancer is being provided. There was a somewhat above-average amount of interest, particularly when compared with that of other non-metropolitan areas, in instruction relating to psychiatry and psychology.

In the north-central coast area (Sonoma County), physicians indicated a need for further instruction in subjects related to heart disease. A number of respondents in this area also indicated an interest in programs in physiology.

Physicians in the south-central coast counties indicated particular interest in additional instruction in the area of cardiovascular diseases. In addition to numerous suggestions in these disease categories, respondents indicated an interest in further courses in electrocardiography techniques and interpretation.

In the non-metropolitan counties in the Sacramento Valley, few respondents indicated a need for additional programs in cardiovascular diseases. An above-average number specified interest in respiratory diseases, in physiology, and in nutritional diseases.

Vascular diseases and cancer were indicated as areas needing additional emphasis by a number of physicians in the North San Joaquin non-metropolitan counties. In addition, an above-average number of respondents indicated interest in further instruction about musculoskeletal and respiratory diseases.

Physicians in South San Joaquin Valley counties specified a need for additional instruction in cardiovascular diseases and in electrocardiographic technique. Few physicians in this area were interested in further instruction about cancer.

A very substantial proportion of respondents in the Sierras would like additional programs in vascular diseases. Another sizable group indicated interest in heart disease or in electrocardiography. An area of concern among physicians in these outlying counties is emergency treatment of accident victims.

Wanted: More Information About Cardiovascular Diseases

Table 4 contains a listing of subjects related to cardiovascular disease. They were indicated by respondents in answer to questions asking them to specify subjects which should be given additional emphasis in programs of continuing medical education. In total, approximately 30 percent of all subjects suggested were generally related to cardiovascular diseases. It is important to note that this list excludes general references to the subject, since they can provide no assistance in focusing attention on areas of unmet physician needs.

The reader should be mindful that although the numbers of physicians in this listing appear small, they represent physicians whose opinions are sufficiently strong to have prompted them to volunteer specific answers to an open-ended question.

The most frequently mentioned individual subject in the area of cardiovascular disease was electrocardiography. It is estimated that at least 350 physicians statewide feel that this area should receive additional emphasis in continuing education programs. The next in order of frequency is the subject of cardiology. A large proportion of these suggestions came from general practitioners. Next in order of frequency were a group of suggestions that additional emphasis be given to discussions of the anatomy of the heart, without specific references to disease entities.

The single cardiovascular disease entity which was most frequently mentioned by respondents was

that of cardiac arrhythmias. It is estimated that over 200 physicians statewide feel strongly that more emphasis should be given this subject. Among other disease entities which were mentioned with some frequency were hypertension, myocardial infarct, arteriosclerosis, and pulmonary heart diseases. Several other disease entities men-

tioned less frequently are also included in the table.

Anti-coagulant drugs constituted a subject of interest to a considerable number of physicians. Among other miscellaneous topics related to cardiovascular disease and suggested by a number of respondents were the subjects of angiography, pacemakers, and hematology.

NEW CMA RELATIVE VALUE STUDIES TO BE PUBLISHED IN SEPTEMBER

A new edition of the *Relative Value Studies* will be published by the California Medical Association in September.

The *Relative Value Studies*, or "RVS," is a complete listing of procedures performed by physicians. There are also unit values which indicate the relationship of values of services to each other.

The RVS will become effective for usage in California 1 April, 1970. It is designed to assist doctors, health insurance carriers, consumers and business to identify procedures which physicians perform. Furthermore, the edition serves as a guide to understanding the basis for charges. However, this is not a fee schedule.

The first edition of the RVS was published in 1956. Its concept has been adopted by other state medical societies and applied to voluntary health insurance and government-financed programs nationwide.

Revised by the California Medical Association's Committee on RVS, the 1969 edition is the culmination of more than two years of intensive study and consultation with experts in the health care profession.

"The content of this edition (of the RVS) reflects as completely as possible the manner in which medicine is practiced in California at this time," William H. Thompson, M.D., Chairman of the CMA Committee on RVS, said.

Major changes are: (1) expansion of the coding system from four to five digits; (2) inclusion of approximately 50 percent more procedures than in the 1964 edition; (3) introduction of the concept of "modifiers"; (4) structuring of each RVS section unit values in such a way as to make them applicable to only that individual section; and (5) reorganization of the musculoskeletal system in the Surgery Section entirely according to body system.

A system of two-digit "modifier" codes for physicians was introduced so they may easily indicate circumstances which may affect the fee charged—either up or down—for a specific procedure.

There are a number of changes in specific sections. For example, in the medicine section, physician visits have been further refined to describe more accurately their relative complexity. New subsections have been added to describe services provided in extended care facilities and in hospital emergency rooms. Also included are many diagnostic services which were formerly included in "Surgery" (such as procedures relating to the eye, ear and the cardiovascular system).

Another major revision is the listing of all vascular injections for radiology in the "Surgery" section only, with cross reference appearing in "Radiology." The "Laboratory" section, now called "Pathology," was reorganized according to the type of procedure performed rather than by the source of the specimen.

More than 20 medical specialty subcommittees and a number of individual consultants—comprising nearly 100 physicians—and representatives of the insurance industry, component medical societies and computerized billing services were consulted "in an attempt to make this edition as useful as possible," Dr. Thompson explained.

The format of the book has been improved with an edge index to make it easier to find and turn to particular sections. The subject index will be more detailed in its listing of procedures.

One copy of the 1969 RVS will be mailed about October 1 to each CMA member free of charge. Additional copies, at \$3.50 each (including tax), will be available from Six-Ninety-Three Sutter Publications, Inc., 693 Sutter Street, San Francisco 94102. Prepaid orders will be filled beginning October 1.

Informed Consent Regarding "The Pill" and New Drugs*

■ *In prescribing certain drugs, it is prudent for the physician to give the patient information on the advantages and disadvantages of the medication. This is especially true when patients request the oral contraceptive, popularly known as "the pill." Because of the sensational publicity relating to possible side effects from the pill, we know from past experience in other similar situations that serious patient questions may arise out of real or fancied effects from use of the pill.*

CMA has prepared two Health Tip articles: one devoted exclusively to the pill, and the other entitled How Does Your Doctor Know When a New Drug Is Safe? The two articles are available in quantity through CMA and are reprinted below. It is suggested that each physician consider giving the two articles to every patient seeking a prescription for the pill, and the drug article to all patients receiving certain other drugs—and in addition, the physician should make an entry in the patient's record of the delivery of the articles. In this fashion, "informed consent" could occur without the physician being required to be a lecturer but with the explanation to the patients being uniform and being done in a friendly, understandable manner. The dissemination of this data by the physician with the corresponding entry in the patient's record has a relationship to the continuation of the physician-patient rapport. The importance of an entry in the patient's record of whatever information you give cannot be overemphasized.

The two articles reprinted here may be ordered in quantity for this purpose at nominal cost from CMA Health Tips. (See Order Blank at end of article.)

What You Should Know About "The Pill"

WOMEN WHO ARE TAKING oral contraceptives — generally referred to as "The Pill" — as a method of birth control do so only under medical supervision, and their doctors usually explain to them at the outset that they may anticipate certain side effects, especially in the first months of use.

From time to time, newspapers and magazines carry sensational articles disclosing "new" revelations of dangers which might be associated with the use of the pill, and the peace of mind of millions of women is shattered. Patients may all too readily forget the careful instructions and reassurances they received from their doctors, and react with panic.

Here are some things doctors *do* know and *do not* know about the pill — at this time.

Our Best Knowledge—At This Time

It is important to remember, first of all, that the pill has been authorized for use only since 1956 — that is, only 13 years. It has been in widespread use only since 1961. This means that no woman has taken the pill through the entire span of her reproductive life — from age 14 to age 50. In other words, what your doctor tells you about the possible risk of taking the pill represents the best that is known to medical science at this time. It is not yet known whether years of taking it might produce adverse effects which are not now anticipated. It is impossible, at this time, to know what the genetic effects of the pill might be on future generations; however, in the best opinion of most doctors, the pill is safe. These medications are the subject of continuing study and observation, and if any results in the future modify the opinions of doctors, they will share that information with their patients.

What, then, can you believe about the effects of the pill?

*Reprinted from *CMA News*, July 1969.

Prepared and released as a public service by the California Medical Association.

Temporary Discomfort

First, it is true that the pill produces a variety of minor discomforts among many women who use it. It should be remembered that the pill acts on the hormonal system, bringing about endocrine changes similar to those which occur during a normal pregnancy. It is logical, therefore, that many of the discomforts which accompany some pregnancies also may accompany the use of the pill. For example, many women using the pill (and many pregnant women) experience nausea and vomiting. Some find that they develop some pigmentation of the skin; others develop acne. (On the other hand, many doctors find the pill very effective in *clearing up* acne.) There is sometimes an excessive amount of vaginal mucous secretion among women taking the pill. Others may experience weight gain. In a certain percentage of women there are emotional effects associated with hormonal changes, whether brought about by pregnancy or by use of the pill. These emotional responses may include depression or decreased or increased sexual drive.

These are all temporary changes. They are not serious or threatening. If they are caused by pregnancy, they disappear when the pregnancy is completed and if they are caused by the pill, they disappear when the pill is discontinued. However, in most cases, the discomforts last only for a few months and the woman prefers to "wait it out" and, if her doctor concurs, she continues to take the pill. Sometimes a change of dosage, under medical supervision, relieves the symptoms.

One side effect of the pill does call for treatment. Yeast vaginitis occurs in about 30 percent of the users, which is approximately the same incidence as in pregnant women. This inflammation is *not* a serious health problem, and it responds well to treatment. Sometimes the treatment can be administered without even discontinuing the use of the pill.

Is "The Pill" Dangerous?

What about rumors of more serious complications resulting from the use of the pill?

The relationship between the pill and cancer has been the subject of many studies. To the best of current knowledge, the pill does not cause cancer of the breast, the cervix, or the body of the uterus. Cervical "*Pap*" smears done on patients who are taking the pill have shown that sometimes

there are tissue changes, but there has not been evidence of the development of cancer. Every woman on the pill should have the *Pap* test done regularly; if her doctor finds any hint of abnormality, he will advise her whether or not to discontinue the pill.

Does the pill cause sterility? About 80 percent of women who are on the pill get pregnant within three months of discontinuing its use when they are ready to have a child. Those who have a difficult time getting pregnant are probably those who were relatively infertile before they started to take the pill.

Does the pill cause malformed babies? The only instances of this have occurred when a woman continued taking the pill *after* she was pregnant. Doctors agree that the pill should not be taken by women during pregnancy.

Finally, what about blood clotting? Here medical opinion seems somewhat divided. Extensive studies have been conducted in both this country and England, and British physicians in recent years have questioned the complete safety of the pill in this respect. This situation is being carefully watched, but medical spokesmen point out that a certain number of all women develop a blood-clotting disease, whether they use the pill or not and that this disease tends to be a complication of pregnancy. In other words, the same women who might develop blood clots while taking the pill might also have developed them during pregnancy. A review of many studies of cause-and-effect relationship between the pill and blood clotting, published in the *Journal* of the American Medical Association of 10 February 1969 revealed only one case of this disease in 27,000 women-years of pill-use (in other words, one case in 2,700 women using it for a period of 10 years). To sum up our knowledge to date, a risk does exist but it is small, unpredictable, and much less than that involved in a pregnancy.

"The Pill" and You

The pill, like every other powerful drug, has different effects on different users. Some women may be particularly sensitive to it, just as some people are sensitive even to aspirin. An individual sensitivity does not always mean that the drug is dangerous. It does mean that the individual patient should discontinue its use.

What should you do about the pill? You should discuss family planning fully with your doctor,

including the various methods available. If he prescribes the pill, you should follow carefully his instructions concerning its use. Tell him promptly about any changes in yourself which you may notice after you start taking the pill. Go back to him for checkups as often as he advises.

How Does Your Doctor Know When a New Drug Is Safe?

In recent years, medical science has made impressive headway in developing new drugs that either prevent or treat diseases which were once life-threatening. Among these achievements have been vaccines, antibiotics, and the cortisone drugs — to cite those which are most widely known. But each step along the way toward controlling disease has been taken slowly and carefully; the process is a painstaking one. Only after a new medication has proved itself through clinical trials will it be licensed for widespread use.

Even after a drug has been authorized as acceptable for use by practicing physicians throughout the country, there always remains some risk in this use. Not all patients react in exactly the same way, and what is entirely safe for one may produce adverse reaction in another. A drug which is highly potent in the treatment of disease is always suspect of causing occasional adverse effects in some patients. Even such a life-saving drug as

penicillin *can* be dangerous for some patients, as some foods are not tolerated by some people.

In giving drugs to patients, the physician takes the responsibility for being familiar with experimental work which has been done with the drug. Whether the drug is new, or tried-and-true, he does not give it indiscriminately. He prescribes only what he thinks will benefit the patient — the beneficial effect far outweighing possible, but very small, risk. Finally, he will continue to watch the patient to detect evidence of side effects to deal with them appropriately.

When your doctor gives you a prescription for a drug you have never used before, and accompanies it with a discussion of its possible risks, he does not intend to alarm you. He is, rather, alerting you. He would not be giving you the medication at all if it were not presumed to be good for you. But he believes that you must share with him the awareness that there might be unforeseen reactions. If the disease being treated is a severe one or has been very resistant to treatment, the patient and the physician are usually more receptive to taking risks. But no significant risk to a patient is ever willingly incurred by the physician. Both physician and patient are, to some extent, at the mercy of the unpredictability of individual responses.

The patient or the parent of the patient should be aware that there is a price, because of these uncertainties, for all improvements in prevention and cure of disease. In explaining potential risks, the physician is seeking the "informed consent" of the patient. The patient must share the responsibility with the physician. When both are aware of this, the course of treatment is likely to go more smoothly.

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EDITORIAL

The New Assistant Secretary

WHEN ROGER EGEGERG gave his paper "The Patient: A Statistic or a Person" at the Annual Meeting of the California Medical Association, and when the editors accepted it for publication in this issue of CALIFORNIA MEDICINE, no one suspected that he would be selected by President Nixon as Assistant Secretary for Health and Scientific Affairs in the Department of Health, Education, and Welfare.

This signal honor to this well-known and respected California physician is a fitting capping to a distinguished career of service in patient care, public health, social welfare and most recently in medical education. Those who know Roger Egeberg are sure that he will leave his mark on the Department of Health, Education, and Welfare just as he has on the California State Board of Health, the Los Angeles Department of Charities, the University of Southern California School of Medicine, and most recently the pace-setting California Committee on Regional Medical Programs.

This forceful and effective administrator has also been a practicing physician and his paper makes clear that he views the patient as a person and not a statistic. This augurs well for the health of the American public as he assumes his important post in Washington, D.C.

Von Willebrand's Disease

VON WILLEBRAND'S DISEASE is probably the most common congenital hemorrhagic disorder affecting mankind. Its most frequent clinical symptom is bleeding from the mucous membranes, particularly after minor operations, and its principal laboratory finding is a long bleeding time. It occurs in both sexes and is transmitted as an autosomal-dominant characteristic. In the present issue of CALIFORNIA MEDICINE Herbert Perkins, participating in the Medical Staff Conference, presents a masterful discussion of the problems involved in the diagnosis and treatment of this disorder, even though improved methods have recently become available.

Since Professor Erick von Willebrand of Helsinki first described this condition in a group of residents of the Aaland Islands in the Baltic Sea in 1926, the variability in the severity of its clinical and laboratory manifestations has been recognized. For many years the diagnosis was based on the finding of a prolonged bleeding time, normal clotting time, normal clot retraction, and a normal number and appearance of the blood platelets; capillary fragility was sometimes increased. As early as 1928, however, George Minot pointed out that the one characteristic positive laboratory finding of the disease, that is, the prolonged bleeding time, might be demonstrable only intermittently; since then there has been a continuing search for other confirmatory diagnostic criteria.

Modern techniques that have improved the accuracy of diagnosis include (1) the use of more sensitive bleeding time methods, such as those of Ivy or Borchgrevink, rather than the Duke method

which is routinely used in most hospital laboratories, (2) the determination of the level of Factor VIII (antihemophilic factor) in the blood plasma, and (3) the use of the Salzman method for the determination of platelet adhesiveness to glass. Unfortunately, while there is good correlation of abnormal findings by these methods with what is thought by the clinician to be von Willebrand's disease, based on all available clinical and laboratory data, there is no single test which is absolutely characteristic of the disease except one which carries with it the risk of transmission of serum hepatitis. The method referred to is the demonstration of a progressive rise of Factor VIII over a period of 24 to 36 hours to far higher plasma levels after transfusion of appropriately prepared platelet-free plasma, cryoprecipitate, serum, or certain plasma protein fractions than can be accounted for by the amount of Factor VIII which they contain.

In the early days when a long bleeding time associated with a normal platelet count was almost the sole criterion for diagnosis, the disorder was undoubtedly missed in many patients who had the disease, and misdiagnosed in others who did not. Even now, with the use of more sophisticated methods the diagnosis may be difficult. The principal conditions to be differentiated are (1) other disorders with moderately low Factor VIII levels such as classic hemophilia of the "mild" variety in the male and some heterozygous carriers of the hemophilic trait in the female, and (2) other hemorrhagic tendencies with long bleeding times, particularly acquired and congenital platelet functional disorders. Some help may be afforded by the use of the aspirin tolerance test, as the characteristic normal bleeding time in the mild hemophilic group is not prolonged beyond the normal range by the administration of aspirin,¹ whereas aspirin will usually definitely prolong a normal or borderline bleeding time in von Willebrand's disease.

There are several findings which may implicate an intrinsic platelet disorder when the bleeding time is prolonged but when the platelet count and level of Factor VIII are within normal limits. Impaired clot retraction that can be improved by the addition *in vitro* of a one-tenth volume of a normal fresh platelet suspension but that is not influenced by the addition of a one-tenth volume of concentrated adenosine diphosphate (ADP) solution, is characteristic of Glanzmann's thrombasthenia. Poor prothrombin consumption or the demonstra-

tion of impaired platelet factor 3 availability by more sensitive techniques suggests "thrombopathia," particularly if many of the platelets are of the large hypergranular variety as described by Bernard and Soulier² in 1948. A more recently described platelet functional disorder³ may require methods of investigation not readily available except in coagulation research laboratories. In this condition the bleeding time is decidedly prolonged and platelet adhesiveness is impaired as in von Willebrand's disease, but the Factor VIII level is within the normal range. The number and appearance of the blood platelets, degree of clot retraction, and platelet aggregation by high molar ADP and thrombin are normal but aggregation by collagen, epinephrine, serotonin, and trypsin is defective. The platelets do not adhere in a normal manner to collagen fibrils. Within a few months after publication of our original case³ we observed three additional patients with this disorder in our laboratory. It appears likely that a systematic survey of patients now diagnosed as having von Willebrand's disease but who have normal Factor VIII levels may reveal many other patients with this disorder. The segregation of von Willebrand's disease from these and other more obscure platelet functional defects has obvious important therapeutic implications. Treatment of such platelet conditions with preparations containing even highly concentrated von Willebrand's factor would be useless; on the other hand, treatment of von Willebrand's disease with large amounts of platelet-rich plasma might prove to be inadequate, for it might not contain enough of the specific plasma factor required.

Despite the development of highly effective concentrates of the von Willebrand factor, such as cryoprecipitate prepared by the method of Pool and Shannon⁴ and Factor VIII preparations made by the Hyland Laboratories, treatment of this disease may be very difficult. This is particularly true in patients with bleeding from the gastrointestinal tract as in a patient previously described by Perkins⁵ and in a female patient who has recently spent many months at the U.S. Army Letterman General Hospital in San Francisco. Some patients are in constant difficulty because of epistaxis, menorrhagia, and other types of spontaneous bleeding, while others bleed only after a surgical challenge. The incidence of surgical bleeding is exceedingly variable even in the same patient. Paradoxically, there is generally less risk of abnormal bleeding in a major operation with large areas of soft tissue

trauma than in a minor procedure involving the mucous membranes, such as a tooth extraction or tonsillectomy.

Should we give prophylactic treatment to all patients with von Willebrand's disease undergoing surgical operation simply because of the ready availability of highly effective concentrates of the von Willebrand factor? I think not; we must guard against the danger of overemphasizing specific replacement therapy. We must remember that plasma and all its derivatives useful in the treatment of this disorder carry the risk of the development of serum hepatitis in the recipient. In earlier days, when treatment was of necessity empirical, our advice to referring surgeons was as follows: (1) Even though the patient has had abnormal surgical bleeding in the past it may very well not happen again, particularly if careful local hemostasis is practiced at the time of operation; (2) the patient must be advised that he has a hereditary hemorrhagic disorder which may cause him to bleed abnormally but he must also be strongly reassured that the chances of his bleeding more vigorously than can be readily controlled by local measures or transfusion are virtually nil (this reassurance in itself may have considerable therapeutic benefit for both the surgeon and the patient); and (3) if abnormal bleeding does occur, use local measures to combat it and transfuse only when there is a clear danger to the patient from blood loss, and then use fresh whole blood if possible. This regime proved effective in most patients and much of the counsel is still valid. However, now fresh noncontact plasma or an appropriate plasma derivative containing the von Willebrand factor should be used instead of fresh whole blood when it is obvious that local hemostatic measures will not suffice.

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Immune Complexes and Disease

IN THE LAST FEW YEARS increasing evidence has come forward for a significant role of antigen-antibody complexes in a wide variety of disorders. The stimulus of the experimental studies of Cochrane and Dixon, summarized in their article in this issue of CALIFORNIA MEDICINE has played a major role in these developments. Thus far the most significant findings concerning a pathogenic role for antigen-antibody complexes have been made in the area of renal disease but a number of other disorders, including rheumatoid arthritis, are currently under investigation from this point of view. Immunological mechanisms in general have proven uniquely difficult to demonstrate conclusively as inciting agents in disease. Even, for example, in the well studied autoimmune thyroiditis the exact process involved in the thyroid injury remains unclear. Much work remains for the clinical investigator in this field before the ubiquity of these mechanisms for human disease can be properly assessed.

A significant role for antigen-antibody complexes in renal injury is now well established in systemic lupus erythematosus (SLE). The close similarity in the pattern of γ globulin distribution to that observed after injection of complexes in experimental animals has been apparent for a number of years. More recently, extensive studies in several laboratories^{1,2} have demonstrated that the DNA-anti DNA system is implicated. Antibodies to DNA aroused considerable interest when they were first described in SLE approximately 12 years ago. However, they were relegated to the position of scientific curiosities, and it has only been recently that their harmful potential has been realized. Antibodies to double stranded DNA have special significance because double stranded DNA antigens can appear in the circulation as a result of tissue breakdown³; antigen-antibody complexes are

formed with fixation of complement and deposition in the most vulnerable organ, the kidney. Elution of antibody from isolated glomeruli of diseased kidneys has proved to be a very effective technique for the detection of antibodies deposited in the kidney.^{1,2} DNA antibody has been found in such eluates at specific concentrations as high as one thousand times those in the serum. DNA antigen has also been demonstrated in the granular deposits observed in the glomeruli. Other more indirect evidence such as the close clinical relationship between the appearance of DNA antibodies, serum complement depression and exacerbations of disease⁴ has also aided in establishing the significance of the DNA system. Further studies are required to determine the relevance of the many other antibodies in the serum of these patients; some of these, if they can encounter specific antigen, may be involved as well.

Another type of renal disease where evidence for immune complexes is rapidly accumulating is that associated with various types of drugs. Some of these may present a picture very analogous to that of serum sickness; in others, chronic drug administration may lead to a slowly progressive glomerulonephritis. The latter situation is well illustrated in the case of penicillamine. Numerous instances of nephritis have been reported following chronic administration of this material for the treatment of cystinuria, Wilson's disease or rheumatoid arthritis. Granular deposits of γ globulin and complement along the glomerular basement membrane are readily visualized in fluorescent antibody studies⁵ which closely resemble those produced in experimental animals by injection of complexes in the work of Cochrane and Dixon. Detailed studies of one such autopsy case in the authors' laboratory have confirmed these findings. The technique of elution of isolated glomeruli has been applied and specific antibody recovered. In most other instances difficulties in the detection of antibodies to many implicated drugs have hampered investigation in this area.

The presence of granular and "lumpy" deposits of γ globulin and complement detected by fluorescent antibody techniques represents presumptive evidence for the accumulation of antigen-antibody complexes in the glomeruli. These may be well visualized in renal biopsy specimens and have been found in a variety of different conditions such as malaria, bacterial endocarditis and thyroiditis. Cases of chronic glomerulonephritis of unknown cause frequently show such a pattern. However,

supporting evidence for specific antigen-antibody complexes is as yet unavailable for most of these. In poststreptococcal nephritis similar characteristics of complex-induced nephritis are present and suggestive evidence for streptococcal antigens in the deposits has been obtained.⁶

Eluates obtained from glomeruli isolated at autopsy from kidneys of patients who had subacute and chronic glomerulonephritis have in a number of instances shown high concentrations of γ globulin. This appears to represent specific antibody but its nature remains a mystery. The search is on in a number of laboratories for specific antigens that might react with such γ globulin. Particular attention is being paid to various human viruses since recent work by Oldstone and Dixon⁷ has demonstrated complexes of virus and antibody in the kidneys of mice with chronic lymphocytic choriomeningitis infection. The task is a difficult one, however, and human tissue antigens, bacterial antigens, and even unknown drugs may be equally reasonable candidates. The possibility also seems likely that multiple antigen-antibody systems are involved in the different cases of idiopathic glomerulonephritis.

Evidence has been obtained that injury to circulating cells, particularly platelets, may be mediated by antigen-antibody complexes. A number of drug induced thrombocytopenias fall into this category. Particular interest is currently centered on similar mechanisms in the joint inflammation of SLE and rheumatoid arthritis. Gamma globulin complexes are well known in the latter and high concentrations have been observed in joint fluid, where they appear to be involved in local complement depletion. Much work remains before a direct cause and effect relationship can be established. Lack of an adequate experimental model similar to those available for immunological renal injury has hampered progress in this field.

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A Midsummer Pipe Dream

MANY ECONOMISTS in both the public and private sectors of society are beginning to espouse restrictions on both physicians and patients as a means of reducing the cost of health care. Since these restrictions on doctors and patients can reduce costs only by curtailing the quality or quantity of services or both, this approach seems a curiously illogical way to move toward the real objective, which everyone agrees should be to increase rather than restrict the quality, quantity and economic efficiency of these services. There must be some better alternative.

The American economy as a whole has a remarkable record of achievement and has produced undreamed of quality, quantity and economic efficiency in business and industry. Its success was built upon incentives, incentives of recognition and reward, incentives of profit. And it was these incentives that produced the results. Restrictions were generally applied only when there was interference with fair competition or with the general good of the populace. Restrictions tend to restrain rather than encourage growth. The national goals for health clearly will require an as yet undreamed of growth in quality, quantity and economic efficiency in every aspect of the production, marketing and delivering of health care services. The parallel of what needs to be done in health care and what has been accomplished in American industry as a whole is impressive. One wonders if the incentives which have been so successful in business and industry could not somehow be made to work better in health care.

Perhaps the time has come to re-examine the national approach to the economics of health care. The traditional idea of medical care as a form of charity is rapidly passing from the scene, and the non-profit approach, which was actually born of charity medicine, seems somehow to lack either the incentive or the ability to meet today's needs for quality or efficiency, although it has generally done well with quality. Government-operated health care programs both here and abroad have proved to be notoriously wasteful and usually subject to a kind of creeping bureaucratic paralysis. From even a cursory examination it would seem that what is lacking and what is needed is to find a way to unleash the enormous energy and resources of the private sector of the American economy and bring these to bear upon the present and as yet undreamed of needs for more quality, more quantity and more efficiency in health care.

To do this would require an almost complete reversal of the present government and public attitudes toward profit in health education and health care. At first this may seem an horrendous suggestion, but perhaps it is not. It may even prove to be a necessary consequence of the demise of the charity approach with all its manifestations in medical care, and the evident inability of government programs to find real solutions to the problems created by the new national expectations for more and better services for more people. There is an interesting and perhaps pertinent precedent in the oil industry, which was encouraged through tax incentives to increase the quality, quantity and efficiency of oil production in order to meet a tremendously rapidly growing national need for oil and oil products. Could it be that here might be found not only the precedent but also the incentive which would provide a better alternative to restriction and restraint in health care, and could it be that the American public and the American government might be persuaded to encourage the American economy by such a device to apply its full energy and resources to finding answers to this national problem which is in urgent need of a better solution?

Hypotension and the Shock Syndrome in Myocardial Infarction

RICHARD S. ROSS, M.D.

Material Supplied by the California Heart Association

HYPOTENSION IS A COMMON and often benign consequence of myocardial infarction while the "shock syndrome" is a less common, but often fatal complication. Precise definition and clear understanding of the hemodynamic consequences of myocardial infarction are, therefore, necessary for management.

Blood pressure alone is not a good index of the patient's clinical status. Blood pressure (BP) is a function of both cardiac output (CO) and total peripheral resistance (TPR) as indicated by the simple relationship:

$$BP = CO \times TPR$$

Thus, BP will be reduced if either CO or TPR is reduced.

Shillingford and colleagues have shown that there are two physiological patterns associated with arterial hypotension depending upon the state of peripheral resistance. In one group of patients, the hypotension is clearly related to a reduced cardiac output and the peripheral resistance may be normal or increased. In the second group, TPR is reduced but the cardiac output is normal. These two groups can sometimes be distinguished clinically. The first group with increased resistance presents with cool extremities and a small pulse volume while the second group is characterized by warm extremities and a full pulse.

Hypotension exists in at least 80 percent of patients following myocardial infarction and in most patients the blood pressure will return to normal levels with the relief of pain and the administration of oxygen. The hypotension occasionally persists for weeks or months, but is often unassociated with significant symptoms.

The Shock Syndrome

The shock syndrome occurs in about 20 percent of patients with myocardial infarction and accounts for at least 50 percent of the deaths now that the mortality from arrhythmias has been reduced. The mortality rate in patients with the shock syndrome secondary to myocardial infarction ranges from 85 to 95 percent if the syndrome is rigidly defined and clearly distinguished from simple hypotension as described above.

The following criteria for the shock syndrome define a population of patients with a mortality of greater than 95 percent. (1) Systolic arterial blood pressure of less than 80 mm Hg, (2) Clinical signs of peripheral circulatory insufficiency; cold, moist skin and cyanosis, (3) Dulled sensorium, (4) Oliguria with urine flow of less than 30 ml/hr, and (5) Failure of improvement to follow relief of pain and the administration of oxygen.

The insult to the heart is the cause of the shock syndrome in myocardial infarction although all organ systems are ultimately involved. The function of the heart is impaired by the initial insult and this results in a decrease in arterial pressure and, hence, coronary blood flow because of its dependence upon aortic perfusion pressure. The reduction in coronary perfusion pressure and myocardial blood flow further impair myocardial function and may increase the size of the myocardial infarction. Arrhythmias and metabolic acidosis also participate in this deterioration in that they are the result of inadequate perfusion and both tend to perpetuate the precipitating conditions. It is this negative feedback relationship (impaired cardiac function—arterial hypotension—reduced coronary blood flow—impaired cardiac function) which accounts for the high mortality associated with the shock syndrome.

Cardiac output is lower in a population of patients with shock than in those who do not have the shock syndrome, but this is by no means the whole explanation. There are many patients with myocardial infarction without shock who have cardiac output in the same range or lower than that measured in patients with shock and, therefore, it is not possible to characterize these patients on the basis of changes of cardiac output alone.

Total peripheral resistance, the other factor important in determining blood pressure, may be either normal increased or decreased in myocardial infarction. Here again, a similar range of values for total peripheral resistance can be seen in pa-

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tients in the absence of shock. Normally, a fall in cardiac output is accompanied by a compensatory rise in total peripheral resistance, but in patients with shock due to myocardial infarction the appropriate response in peripheral resistance fails to occur. Thus, it appears that the total peripheral resistance is inadequate to support blood pressure at the existing level of cardiac output, regardless of the extent of reduction of the latter.

Treatment

The objective of treatment is the interruption of the negative feedback loop whereby impaired myocardial function leads to a reduction in arterial pressure, decreased coronary blood flow and a further depression of left ventricular function. This objective is approached by attempting to improve cardiac function and to raise the arterial blood pressure.

Vasopressors constitute an important form of therapy for shock of myocardial infarction. A small increase in arterial pressure may result in a sizable increase in coronary blood flow. The best vasopressors for use in myocardial infarction are norepinephrine (Levophed®) and metaraminol (Aramine®) which act both on the alpha receptors in the arterial wall and also on the beta receptors in the myocardium. Thus, the practical experience with the treatment of shock in myocardial infarction is consistent with the theory of pathogenesis which emphasizes the dual nature of the pathophysiology in that drugs which act on both the heart and the peripheral circulation are the most effective.

Consideration of the central role of impaired myocardial function in the shock syndrome leads to the conclusion that cardiac glycosides should be administered to all patients with this condition. Obviously, the cardiac glycosides cannot improve the function of necrotic myocardium, but a positive inotropic influence of the non-infarcted myocardium is desirable. It has been demonstrated that the incidence of arrhythmia and cardiac rupture is no higher in patients with myocardial infarction treated with digitalis than in a control group.

Certain general measures have proven useful in the treatment of the shock syndrome. All patients with the shock syndrome should receive 100 percent oxygen continuously because the addition of dissolved oxygen to the plasma helps to combat the hypoxemia which is universally present. The relief of pain is important as some vasodepressor reflex activity may be a response to severe pain, but narcotics should be used cautiously in view of their hemodynamic effects. Fluid volume replacement has a limited, but definite, place in the therapy of the shock syndrome due to myocardial infarction. It may be indicated in patients who have been receiving pressor drugs for a prolonged period because pressor therapy results in a decrease in plasma volume secondary to the movement of fluid into extravascular space. In such patients, if central venous pressure is low and there is no evidence of pulmonary congestion, the blood pressure may be easier to maintain after plasma volume has been expanded by the administration of plasma or salt poor albumin. Venous pressure should be monitored and the lungs examined frequently during the administration of plasma. Also, fluid replacement is necessary in patients who have lost extracellular fluid volume consequent to vomiting or sweating.

The high mortality and relative ineffectiveness of conventional therapy has provided the stimulus for the investigation of other approaches to the problem. The basic defect in the shock syndrome is impaired myocardial function and, therefore, many mechanical assist devices are currently under investigation. The therapeutic value of hyperbaric oxygen therapy is also under study. Studies with experimental animals are encouraging, but clinical trials have been disappointing. A large fraction of patients with the shock syndrome have severe, diffuse coronary atherosclerosis with large areas of infarcted myocardium. It is in this group of patients that total replacement of the heart by a homotransplant or an artificial device will have its greatest potential usefulness. Circulatory assist devices may have their greatest use in sustaining life until this is possible.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

BLANCHARD, THOMAS LOFTIN, San Jose. Died 8 June 1969 in San Jose of cancer of the lung, aged 82. Graduate of Cooper Medical College, San Francisco, 1909. Licensed in California in 1910. Doctor Blanchard was a member of the Santa Clara County Medical Society.

❖

BUCK, RONALD M., Santa Ana. Died 17 May 1969 in Orange of abdominal cancer, aged 56. Graduate of Northwestern University Medical School, Chicago, 1939. Licensed in California in 1957. Doctor Buck was a member of the Orange County Medical Association.

❖

BURNAP, SIDNEY R., Cornwall, Connecticut. (Formerly Los Angeles and Santa Barbara.) Died 30 May 1969 in New Haven, Conn., of cerebral hemorrhage, aged 85. Graduate of Columbia University College of Physicians and Surgeons, New York City, 1909. Licensed in California in 1922. Doctor Burnap was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

❖

COUGHLIN, WILLIAM FRANCIS, Carmel. Died 9 May 1969 in Carmel, aged 68. Graduate of Tufts College Medical School, Boston, 1926. Licensed in California in 1938. Doctor Coughlin was a member of the Monterey County Medical Society.

❖

EDMUNDS, DAVID GARTH, Garden Grove. Died 28 June 1969 in Garden Grove of coronary artery disease, aged 50. Graduate of Utah College of Medicine, Salt Lake City, 1945. Licensed in California in 1951. Doctor Edmunds was a member of the Orange County Medical Association.

❖

GALLAGHER, HIRAM M., Los Angeles. Died 27 June 1969 in Los Angeles of congestive heart failure, aged 81. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1911. Licensed in California in 1914. Doctor Gallagher was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

GARD, KEITH L., Carmichael. Died in a plane crash near Benicia, 19 June 1969, aged 45. Graduate of Kansas City College of Osteopathy and Surgery, Kansas City, Mo., 1957. Licensed in California in 1958. M.D. degree from California College of Medicine, 1962. Doctor Gard was a member of the Sacramento County Medical Society.

❖

GIDOLL, SIDNEY H., San Francisco. Died 21 June 1969 in San Francisco, aged 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1923. Licensed in California in 1923. Doctor Gidoll was a member of the San Francisco Medical Society.

❖

HALL, JOHN ELWIN, Malibu. Died 15 June 1969 in Palm Springs, aged 54. Graduate of the University of Southern California School of Medicine, Los Angeles, 1942. Licensed in California in 1942. Doctor Hall was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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HAWTHORNE, JOHN JAY, Vallejo. Died 11 June 1969 in Vallejo, aged 58. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, 1935. Licensed in California in 1937. Doctor Hawthorne was a member of the Solano County Medical Society.

❖

JACKSON, JOHN LIVINGSTON, Pasadena. Died 27 June 1969 in Pasadena of cancer of the pancreas, aged 65. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1930. Licensed in California in 1930. Doctor Jackson was a member of the Los Angeles County Medical Association.

❖

JACOBSON, LELAND CARL, San Bernardino. Died 29 May 1969 in San Bernardino, aged 63. Graduate of the University of Southern California School of Medicine, Los Angeles, 1937. Licensed in California in 1937. Doctor Jacobson was a member of the San Bernardino County Medical Society.

❖

KAGAN, HARVEY D., Los Angeles. Died 25 February 1969 in Los Angeles of massive myocardial infarction, aged 55. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1937. Licensed in California in 1937. M.D. degree from California College of Medicine, 1962. Doctor Kagan was a member of the Forty First Medical Society.

❖

KAPLAN, SAMUEL, Sherman Oaks. Died 20 June 1969 in Beverly Hills, aged 68. Graduate of Long Island College of Medicine, New York, 1927. Licensed in Cali-

fornia in 1948. Doctor Kaplan was a member of the Los Angeles County Medical Association.

✧

MANDRUSSOW, VECESLAV ALEXANDER, San Francisco. Died 10 June 1969 in San Francisco of heart disease, aged 49. Graduate of Ludwig-Maximilians-Universität Medizinische Fakultät, München, Bavaria, Germany, 1947. Licensed in California in 1953. Doctor Mandrusow was a member of the San Francisco Medical Society.

✧

MILLER, HYMAN, Beverly Hills. Died 25 June 1969 in Los Angeles, aged 71. Graduate of Stanford University School of Medicine, Palo-Alto-San Francisco, 1922. Licensed in California in 1922. Doctor Miller was a member of the Los Angeles County Medical Association.

✧

MINER, SABIN SAMUEL, Lakewood. Died 31 May 1969 in Lakewood of acute myocardial infarction, aged 60. Graduate of the University of Colorado School of Medicine, Denver, 1944. Licensed in California in 1948. Doctor Miner was a member of the Los Angeles County Medical Association.

✧

MOORE, MARVIN HARRISON, Fresno. Died 7 June 1969 in Fresno, aged 65. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Doctor Moore was a member of the Fresno County Medical Society.

✧

MOORE, WILLIAM GEORGE, San Rafael. Died 17 June 1969 in San Francisco, aged 91. Graduate of University of California Medical School, Berkeley-San Francisco, 1900. Licensed in California in 1900. Doctor Moore was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✧

MURPHY, JOHN MATTHEW, Hayward. Died 27 June 1969 in Hayward of cerebral thrombosis, aged 68. Graduate of the University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Doctor Murphy was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✧

NAGELMANN, CLEMENS VERNARD, Santa Barbara. Died 19 June 1969 in Santa Barbara, aged 88. Graduate of Creighton University School of Medicine, Omaha, 1909. Licensed in California in 1918. Doctor Nagelmann was a member of the Santa Barbara County Medical Society, a life member of the California Medical Association, and a member of the American Medical Association.

PEARSON, LANIER NEVILLE, Fresno. Died 4 February 1969 in Fresno of cerebral vascular accident, aged 64. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1928. Licensed in California in 1928. M.D. degree from California College of Medicine, 1962. Doctor Pearson was a member of the Fresno County Medical Society.

✧

ROTHMAN, PHILLIP ELIAS, Los Angeles. Died 4 June 1969 in Honolulu, Hawaii, of coronary thrombosis, aged 68. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1925. Licensed in California in 1927. Doctor Rothman was a member of the Los Angeles County Medical Association.

✧

SANFORD, JAMES ROBERT, Solana Beach Park. Died 18 June 1969 in Pasadena of gastrointestinal hemorrhage, aged 79. Graduate of Vanderbilt University School of Medicine, Nashville, Tenn., 1916. Licensed in California in 1923. Doctor Sanford was a member of the Los Angeles County Medical Association.

✧

SANTOS, CRISOSTOMO C., La Habra. Died 4 October 1968 in La Habra of coronary occlusion, aged 46. Graduate of the University of Santo Tomas Faculty of Medicine and Surgery, Manila, P.I., 1948. Licensed in California in 1961. Doctor Santos was a member of the Orange County Medical Association.

✧

SASLAW, EDWARD WITAMAN, Daly City. Died 12 June 1969 in San Francisco, aged 56. Graduate of the University of Colorado School of Medicine, Denver, 1947. Licensed in California in 1949. Doctor Saslaw was a member of the San Francisco Medical Society.

✧

SAUL, WALTER, Santa Ana. Died 22 June 1969 in Orange, aged 69. Graduate of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, 1924. Licensed in California in 1938. Doctor Saul was a member of the Orange County Medical Association.

✧

STARKS, DOROTHY JOHANNA, Menlo Park. Died 18 June 1969 in Palo Alto, aged 68. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1928. Licensed in California in 1928. Doctor Starks was a member of the Santa Clara County Medical Society.

✧

SULLIVAN, WALTER JAMES, Beverly Hills. Died 26 June 1969 in Los Angeles of pneumonia, aged 79. Graduate of Northwestern University Medical School, Chicago, 1915. Licensed in California in 1926. Doctor Sullivan was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H. Director, State Department of Public Health

Northern California Epilepsy Program

THE DAYS OF STONING EPILEPTICS have passed but general enlightenment about epilepsy is still a hope for the future, particularly a hope of those affected by episodes of dysrhythmic brain electrical activity.

Physicians now know epilepsy to be a symptom complex, but the general public still thinks of it as a single disease entity. The knowledge of too many persons is a mixture of fact and fiction, more often weighted on the side of fiction. Until the effects of old superstition and myth are dispelled, the epileptic will continue to be a target of fear and prejudice.

Because of the propensity to hide epilepsy, good prevalence figures and studies of treatment effectiveness are hard to obtain. A State Department of Public Health study estimated in 1963 that between 62,000 and 85,000 out of the state's then population of seventeen million had epilepsy.¹ The disturbing symptoms of many of these persons with either major or minor seizures or a combination can be controlled by medication. It is commonly estimated that with drug therapy 50 percent of epilepsy patients become seizure-free, 25 percent achieve decided improvement (reduction in number and severity of seizures) and the remaining 25 percent pose a difficult problem for the practitioner.

Questionable, complicated and refractory cases require considerable time and effort, taxing the physician's patience as well as his skill and knowledge. A study of neurological disorders by the Department in 1964 indicated that coordinated, comprehensive services including social work services were necessary for some patients with major neurological disorders.² Based on these and other findings of both the 1963 and 1964 studies, the Department developed and submitted a project grant application to the United States Public Health Service for a case management study. The grant award was made for a four-year period beginning 1 July 1967 to test the effectiveness of comprehen-

sive services, education and follow-up by a multidiscipline team in controlling seizures and rehabilitating persons with problem cases of epilepsy. The State Department of Public Health has contracted with the Department of Neurology, University of California San Francisco Medical Center, to operate this Northern California Epilepsy Program.

A neurologist, a social worker, and a public health nurse constitute the basic team. A psychiatrist participates in every case conference, making recommendations and deciding from the findings presented whether the patient under discussion needs to be seen by him. Additional team members are available on call from specialties of psychology, neurosurgery, pediatrics, internal medicine, clinical pharmacology, vocational rehabilitation and other fields as indicated by the needs of each patient. Another team member and an important one is the referring physician. Those who have been able to attend team conferences have found the experience stimulating and useful.

What kind of patient has been referred to the program? Of the first 100 patients, 50 were male and 50 female. They ranged in age from under 3 to 65 years, and almost every one had a history of unsatisfactory response to drug therapy. The outpouring of family, social, psychological, educational and vocational problems has astonished a prepared and experienced staff. The problems presented have buttressed the premises upon which the project was based—that refractory epilepsy is complex in its nature and requires a multidisciplinary approach.

What does the team do for these patients? Individual evaluations, carefully prepared by each of the professional disciplines, are discussed and reconciled in case conferences and plans made for any further diagnostic procedures or change in the treatment regime needed. The program undertakes limited term treatment only when necessary and then returns the patient to the referring physician and to other appropriate treatment resources such as social or family service agencies, foster home placement, hospital, psychiatric treatment for patient and family, or vocational rehabilitation

programs. If the patient has no physician, every effort is made to secure one for him.

As the program nears its midpoint, it is clear that a team of medical and paramedical specialists working together to provide comprehensive services to patients and their families in difficult cases of epilepsy can offer benefit in the control of seizures. For some patients, modifying the environment may be as important as adjusting medications.

How can we achieve control of difficult epilepsy cases? If they are not entirely controlled by direct medical procedures, is there a possibility that a

social worker or public health nurse may help by relieving social, family or economic pressures? By the end of the project, enough problem epilepsy cases will probably have been seen and studied to answer many questions and to indicate the likelihood of rehabilitating persons with resistant cases, and the best means of doing so.

REFERENCES

1. California State Department of Public Health: Children With Epilepsy and the California Crippled Children Services Program, Berkeley, California State Department of Public Health, 1963. California State Department of Public Health, Berkeley, 1963.
2. California State Department of Public Health: Neurological and Sensory Disease in California, 1964.

CLUES TO PHLEBOTHROMBOSIS

"In contrast to the clinical picture in thrombophlebitis, the clinical picture in phlebothrombosis is . . . very indefinite. There's nothing that occurs so insidiously as a phlebothrombosis. It takes the alert physician to detect it. There is a tachycardia, and this tachycardia is out of proportion to everything else. The Germans have described this as a step-ladder pulse. The disproportion between the temperature curve, which is usually not high, and the increasing pulse rate should make one alert. There's an apprehension. Now this is difficult to understand; it's difficult to describe; but it's just as real as a leukocytosis. Patients have a sense of impending disaster; and rightly so, because these people are potential fatalities. Now there may be calf or plantar tenderness; but in 40 percent of the cases there is not. And there's an increased erythrocytic sedimentation rate, though this isn't of much significance because many people who are ill have increased sedimentation rates."

—ALTON OCHSNER, M.D., New Orleans

Extracted from *Audio-Digest Surgery*, Vol. 15, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Postgraduate Course Information

CMA:	California Medical Association For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
LLU:	Loma Linda University For information contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
PMC:	Pacific Medical Center For information contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
STAN:	Stanford University For information contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5940.
UCD:	University of California, Davis For information contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0335.
UCI:	University of California — California College of Medicine, Irvine For information contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
UCLA:	University of California, Los Angeles For information contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
UCSD:	University of California, San Diego For information contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
UCSF:	University of California, San Francisco For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
USC:	University of Southern California For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

CANCER

September 17-18—**Cancer Symposium.** Alumni Association, LLU School of Medicine; California Academy of General Practice, Los Angeles Chapter; and American Cancer Society, Los Angeles Branch and California Division at Ambassador Hotel, Los Angeles. Wednesday-Thursday. Contact: Alumni Postgraduate Convention, 1832 Michigan Avenue, Los Angeles 90033. (213) 262-2173 or (415) 885-5822. \$30.

September 20—**Current Concepts in Cancer.** UCSF at Children's Hospital, San Francisco. Saturday.

September 26-27—**Cancer: Concepts and Controversy—Fifth Annual Cancer Symposium.** American Cancer Society, Sacramento Branch and California Division, UCD and CRMP Area II at Sahara Tahoe Hotel, Stateline, Nevada. Friday-Saturday. Contact: Richard K. Wertz, M.D., Symposium Chairman, 916 11th St., Sacramento 95814. (916) 446-7933.

September 26-27—**Current Concepts in Medical Oncology.** Medical Oncology Service, Mt. Zion Hospital and Medical Center at Mt. Zion Hospital, San Francisco. Friday-Saturday. Contact: Ernest H. Rosenbaum, M.D., Director, Medical Oncology Service, Mt. Zion Hospital and Medical Center, 1600 Divisadero, San Francisco 94115. (415) 567-6600. \$30.

October 4—**American Cancer Society, California Branch—Annual Scientific Program** at Hilton Inn, San Diego, Saturday. Contact: Forrest Willett, M.D., Medical Director, ACS, Calif. Div., 875 O'Farrell, San Francisco 94109. (415) 885-5822.

October 17-18—**Preoperative and Postoperative Radiation Therapy in the Treatment of Cancer—Fifth Annual San Francisco Cancer Symposium.** Zellerbach Saroni Tumor Institute and Dept. of Surgery, Mount Zion Hospital and Medical Center at St. Francis Hotel, San Francisco. Friday-Saturday. Contact: Mrs. Barbara Reynolds, Symposium Sec., Mt. Zion Hospital, 1600 Divisadero, San Francisco 94115. (415) 922-3823. \$40.

November 15-16—**Fifth Annual Clinical Cancer Conference.** UCSF. Saturday-Sunday.

December 7—**California Tumor Tissue Registry—Semi-Annual Cancer Conference.** Beverly Hilton Hotel, Beverly Hills. Sunday. Contact: W. K. Bullock, M.D., Exec. Dir., Los Angeles County Hospital, 1200 N. State St., Los Angeles 90033.

December 13—**Radiotherapy Symposium—Lymphomas & Hodgkin's Disease.** Southern California Permanente Medical Group at Ambassador Hotel, Los Angeles. Saturday, 8:30 a.m.-3:30 p.m. Contact: Shirley Gach, Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

MEDICINE

September 13-19—**American Electroencephalographic Society.** El Cortez Hotel, San Diego. Saturday-Friday. Contact: Philip T. White, M.D., 8700 W. Wisconsin Ave., Milwaukee 53226.

September 14-20—**International Congress of Electroencephalography & Clinical Neurophysiology.** El Cortez Hotel, San Diego. Sunday-Saturday. Contact: Richard D. Walter, M.D., Congress Sec. UCLA.

September 19—**The Current Status of Anti-Fertility Agents.** Family Planning Centers of Greater Los An-

- geles at Los Angeles County Medical Association Auditorium. Friday. Contact: LACMA, 1925 Wilshire Blvd., Los Angeles 90057. (213) 483-1581.
- September 19-20 — **19th Annual Professional Symposium on Cardiovascular Diseases.** San Diego County Heart Association in cooperation with UCSD at Hilton Inn, San Diego. Contact: James C. Jordan, M.D., 3545 Fourth Ave., San Diego 92103. (714) 295-4168.
- September 20—**13th Annual Symposium on Cardiovascular Disease.** Ventura and Santa Barbara Counties Heart Associations at Biltmore Hotel, Santa Barbara. Saturday 9-5:00. Contact: Santa Barbara County Heart Assoc., 18 La Arcada Court, Santa Barbara 93104. (805) 963-1541. \$15.
- September 26-28—**Diseases of the Colon and Anorectum.** UCLA at Wadsworth V.A. Hospital, Los Angeles. Thursday-Saturday.
- September 27—**Lesions of the Mouth.** PMC. Saturday.
- September 29 - Oct. 10 — **Intensive Review of Internal Medicine.** USC. Monday-Friday. Two weeks. \$150.
- October 1-3 — **Annual Postgraduate Symposium on Heart Disease.** St. Francis Hotel, San Francisco. Wednesday-Friday. Contact: Gene C. Taylor, Executive Director, San Francisco Heart Assoc., 259 Geary Street, San Francisco 94102. (415) 982-5753.
- October 1-3—**Respiratory Disease: Physiological Basis of Diagnosis and Treatment — 6th Annual Postgraduate Course on the Evaluation of Pulmonary Function.** TB and Respiratory Disease Association of California at UCLA. Wednesday-Friday. Contact: TB and Respiratory Disease Assoc. of California, 424 Pendleton Way, Oakland 94621. (415) 636-1756.
- October 3-4—**Pulmonary Disease in Childhood.** Children's Hospital of Orange County, Orange. Friday-Saturday. Contact: William Taylor, M.D., Program Coordinator, Orange County Medical Center, 101 Manchester Avenue, Orange.
- October 4—**Shock.** Woodland Clinic Medical Group, Woodland. Saturday, 9-4:30. Contact: R. C. Edmondson, M.D., Chairman, Professional Day, Woodland Clinic Medical Group, 1207 Fairchild Court, Woodland 95695. (916) 662-4641.
- October 4—**Inhalation Therapy: Theory and Applications.** American Thoracic Society, California Thoracic Society and TB and Respiratory Disease Association of California at UCLA. Saturday. Contact: TB and Respiratory Disease Assoc. of California, 424 Pendleton Way, Oakland 94621. (415) 636-1756.
- October 7 — **Evening Lectures in Medicine.** UCSF at Oakland Hospital. Tuesday evenings through Dec. 2.
- October 10-12—**California Society of Internal Medicine—Scientific Program.** Coronado. Friday-Sunday. Contact: Cynthia Bell, Exec. Sec., 350 Post Street, San Francisco 94108. (415) 362-1548.
- October 18—**Arrhythmias.** PMC. Saturday.
- October 23—**Hypertension.** USC at Hilton Hotel, Los Angeles. Thursday.
- October 29-30—**Symposium of Diabetes.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday.
- October 31 — **Endocrinology — 14th Annual Medical Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals. Friday. Contact: Shirley Gach, Symposium Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.
- November 7-8—**Physical Medicine and Rehabilitation.** UCSF. Friday-Saturday.
- November 8-9—**Manipulative Medicine.** USC. Saturday-Sunday. \$50.
- November 13—**Office Dermatology.** USC. Wednesday.
- November 13-15—**West Coast Allergy Society.** Hilton Inn, San Diego. Thursday-Saturday. Contact: Betty J. Jones, Exec. Sec., P.O. Box 42067, Portland, Ore. 97242.
- November 15—**Gastroenterology.** PMC. Saturday.
- December 2-5—**Reticuloendothelial Society—6th Annual Meeting.** Jack Tar Hotel, San Francisco. Tuesday-Friday. Contact: Ernest L. Dobson, Ph.D., General Chairman, Donner Laboratory, University of California, Berkeley 94720.
- December 4-6—**Cardiovascular Therapeutics.** American Heart Association in cooperation with UCSD at UCSD. Thursday-Saturday. Contact: Eugene Braunschweig, M.D., Professor and Chairman, Dept. of Medicine, UCSD.

Grand Rounds—Medicine

Tuesdays

9-10:30 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Wednesdays

Grand Rounds in Internal Medicine. 10:30-12:00 noon. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

Grand Rounds in Internal Medicine. 12:30-1:30 p.m., University Hospital, UCSD.

Grand Rounds in Internal Medicine. 1:30-3:00 p.m., Fresno General Hospital.

Thursdays

10:30-12:00 noon, Room C3-105, UCLA Medical Center. UCLA.

Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

2-3:00 p.m., Classroom, Third Floor, Fresno General Hospital, Fresno. CRMP Area IV.

Rheumatology Grand Rounds. 11:30 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

OBSTETRICS AND GYNECOLOGY

September 25-27 — **The Office Practice of Ob/Gyn.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

December 5-6—**Obstetrics & Gynecology.** PMC. Friday-Saturday.

PEDIATRICS

September 19-20—**Pediatric Annual Meeting—Medical Staff, Children's Hospital, Oakland.** Highland Inn, Carmel. Friday-Saturday. Contact: Miss Inetta Carty, Children's Hospital, 51st and Grove Streets, Oakland 94609. (415) 654-5600.

September 24-25—**26th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Kenneth O. Williams, M.D., Sec.-Treas., P.O. Box 2022, Inglewood 90305.

September 29-Oct. 10—**Mental Retardation Workshop.** UCLA. Monday-Friday, Two weeks.

October 1-2—**38th Annual Fall Symposium and Second Annual George C. Griffith Lectureship Dinner.** Los Angeles County Heart Association at Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: Los Angeles County Heart Association, 2405 West Eighth St., Los Angeles 90057. (213) 385-4231.

October 4-5—**Pediatric Neurology.** UCLA. Saturday-Sunday.

October 6-10—**Pediatric Allergy.** UCSF. Monday-Friday.

October 15—**Newborn Infant Care.** USC. Wednesday.

November 8-9—**Pediatric Neuroradiology.** UCLA. Saturday-Sunday.

November 10-12—**The Fetus and the Newborn.** American Academy of Pediatrics at UCSF. Monday-Wednesday. Contact: William H. Tooley, M.D., 327 Crestmont Dr., San Francisco 94131. (415) 566-7637.

December 6-7—**Second Annual Children's Hospital Medical Center Symposium.** Memorial Hospital of Long Beach, Long Beach. Saturday-Sunday. Contact: Norman R. Nager, Director of Public Relations, Memorial Hospital of Long Beach, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

Grand Rounds—Pediatrics

Tuesdays

8:30-9:30 a.m., Sixth Floor Conference Room, Harbor General Hospital, Torrance. UCLA.

8:30 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Conference Room, Sixth Floor, Harbor General Hospital, Torrance. CRMP Area IV.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and the Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Stanford University Medical Center, Palo Alto.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

PSYCHIATRY

September 27-28—**Schizophrenia—Disease, Syndrome, or a Way of Life?** UCSF at Mendocino. Saturday-Sunday.

September 27-28 and October 11-12 — **Intermediate Methods in Family Therapy.** UCSF and San Joaquin County Mental Health Services at Stockton. Saturday-Sunday.

October 7—**Psychiatry and Civil Law.** UCLA. Tuesdays through Dec. 9.

October 18-19 — **Adcsittitious Therapies in Psychiatry.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday.

October 20-24—**Group Therapy.** UCSF at V.A. Hospital, San Francisco. Monday-Friday.

October 24-26—**Southern California Psychiatric Society—Annual Convention.** Biltmore Hotel, Santa Barbara. Friday-Sunday. Contact: Mark F. Orfirer, M.D., 2200 Santa Monica Blvd., Santa Monica 90404.

October 28-Nov. 2—**American Society of Clinical Hypnosis—12th Annual Scientific Meeting and Workshop.** Jack Tar Hotel, San Francisco. Tuesday-Sunday. Contact: F. D. Nowlin, Exec. Sec., 800 Washington Ave., S.E., Minneapolis 55414.

November 1—**The Context of Marriage.** UCSF. Saturday.

November 1-2—**The Problem of Alcoholism.** UCSF Saturday-Sunday.

November 11-16—**Society for Clinical and Experimental Hypnosis—21st Annual Meeting.** Stanford University, Palo Alto. Tuesday-Sunday. Contact: Mrs. Mario Kenn, Society for Clinical and Experimental Hypnosis, 353 W. 57th St., New York 10019.

November 15-16—**Modern Theories in Psychiatry.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

December 6-7—**Therapy in Groups.** UCSF at Mendocino. Saturday-Sunday.

December 13-14—**Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton. Saturday-Sunday.

SURGERY

September 4-6—**Scoliosis Research Society.** Disneyland Hotel, Los Angeles. Thursday-Saturday. Contact: William J. Kane, M.D., Sec.-Treas., Box 484, University Hospitals, Minneapolis 55455.

September 8—**Spine Mechanics—Orthopedic Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals. Statler Hilton Hotel, Los Angeles. Monday, 2-5:30 p.m. Contact: Shirley Gach, Symposium Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

September 13—**Hand Injuries.** PMC. Saturday.

October 3-4—**Vascular Surgery.** UCSF. Friday-Saturday.

October 4—**Ophthalmology.** PMC. Saturday.

October 6-10—**American College of Surgeons—Annual Meeting.** Fairmont Hotel, San Francisco. Monday-Friday. Contact: John Paul North, M.D., 55 E. Erie Street, Chicago 60611.

October 14-22—**Pan-Pacific Surgical Association—11th Congress.** Hawaiian Hilton, Honolulu. Tuesday-Wednesday. Contact: Mrs. Harriet N. DeVault, Exec. Sec., Rm. 236, Alexander Young Bldg., Honolulu 96813.

October 23-26—**American Society of Anesthesiologists—Annual Session.** Hilton Hotel, San Francisco. Saturday-Wednesday. Contact: John W. Andes, Exec. Sec., 515 Busse Highway, Park Ridge, Ill. 60068.

October 31-Nov. 1—**Surgical Emergencies.** PMC. Friday-Saturday.

December 4-6—**Diagnosis and Management of Uveitis—Annual Proctor Foundation Program.** UCSF. Thursday-Saturday.

December 12-14—**Fluid & Electrolytes.** USC at Palm Springs. Friday-Sunday.

Grand Rounds—Surgery

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

9:30 a.m., Neuroradiology, 10:15 Neurology, 11:15 Neurosurgery. Stanford University Medical Center, Palo Alto.

Saturdays

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

OF INTEREST TO ALL PHYSICIANS

September 18-20—**Annual Postgraduate Assembly—Birth Defects.** St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: John C. Eagan, M.D., Director, St. John's Hospital Postgraduate Assembly, 1328 22nd St., Santa Monica 90404.

September 22, 23, 24-Oct. 13, 14, 15—**Annual Postgraduate Circuit Courses.** CMA and STAN weekly at Mt. Shasta, Chico and Auburn. Contact: CMA.

September 24—**Clinical Psychiatry for Non-Psychiatrists: A Course in Medical Psychotherapy.** UCSF. Wednesdays through Dec. 17.

September 25-27—**Initial Emergency Care.** UCSF and American Association of Orthopaedic Surgeons. Thursday-Saturday.

October 2—**A Course in Mental Retardation for Physicians.** UCSF. Thursdays through May 21.

October 9 - Nov. 13—**Freedom of Choice.** UCSF. Thursday evenings.

October 11-12—**Health of the School Child.** UCSF. Saturday-Sunday.

October 11-12—**Kern Postgraduate Conference.** Kern County General Hospital at Civic Auditorium, Bakersfield. Saturday-Sunday. Contact: George A. Paulsen, M.D., Conference Committee Chairman, 2603 G St., Bakersfield 93301. (805) 327-7637.

October 17-18—**Thirteenth Annual Western Industrial Health Conference.** Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Mr. B. H. Bravinder, 2180 Milvia St., Berkeley 94704.

October 17-18—**Western Industrial Medical Association.** Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Mr. B. H. Bravinder, 2180 Milvia St., Berkeley 94704.

October 24-25—**Recreation in Rehabilitation.** UCSF. Friday-Saturday.

October 25-26—**How the Patient Affects the Doctor.** UCSF at Fresno Community Hospital, Fresno. Saturday-Sunday.

November 2-5—**California Academy of General Practice—21st Annual Scientific Assembly.** Century Plaza Hotel, Los Angeles. Sunday-Wednesday.

November 15—**Mayo Alumni Association—45th Annual Meeting.** Century-Plaza Hotel, Los Angeles. Saturday. Contact: Office of the 45th Annual Meeting, 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

November 15-16—**Financial, Tax and Investment Planning.** UCLA. Saturday-Sunday.

November 15-16—**Sex and the Professional Man.** Christian Medical Society at Monte Corona Conference Grounds, Lake Arrowhead. Saturday-Sunday. Contact: Albert Holt, M.D., 4080 Hoking Way, Los Angeles 90027.

December 3—**Postgraduate Assembly—St. Luke's Hospital of Pasadena.** At the Huntington-Sheraton Hotel, Pasadena. Wednesday. Contact: W. K. Bullock, M.D., Chairman, 1969 Postgraduate Assembly, 2632 E. Washington Blvd., Pasadena 91107.

CONTINUOUSLY

Basic Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

SITUATIONS WANTED

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PRACTICES WANTED

OPHTHALMOLOGICAL PRACTICE (medical or surgical) for purchase or association. Southern (or northern) California. Interview now. Available Jan. 15th. Details confidential. Box 9184, California Medicine.

References and Reviews

Science, Washington

Congenital Syphilis—R. C. V. Robinson (714 York Rd., Towson, Md.), Arch. Derm. 99:599-610 (May) 1969.

Treatment of maternal early syphilis in the latter half of pregnancy constitutes treatment of intrauterine congenital syphilis, not prevention. Most stigmas described in the literature may occur in other conditions and are etiologically indistinguishable. Only clinically characteristic interstitial keratitis, mulberry molars, and upper central incisors of the second dentition as described by Hutchinson may be classed as pathognomonic of late congenital syphilis. Stigmas which may be highly suggestive are embryonic pigmentary retinopathy, paroxysmal cold hemoglobinuria, characteristic facies, and Clutton's joints.

Leukemia in Close Relatives—F. W. Gunz and A. M. O. Veale (Christchurch Hosp., Christchurch, New Zealand), J. Nat. Cancer Inst. 42:517-524 (March) 1969.

Leukemia was more common among first-degree relatives of patients with chronic lymphocytic leukemia than could be expected from the incidence of the disease in the population of New Zealand. This confirms earlier results which showed a similar, though smaller, increase in leukemia incidence in all classes of relatives of patients with all forms of leukemia. Laboratory studies indicated a diminished serum γ -globulin concentration and an unusual serum haptoglobin distribution in the leukemia patients. The familial aggregations appear to have been determined at least partly by genetic factors, but the precise mechanism by which they were produced is not known.

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Books received by CALIFORNIA MEDICINE are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.

THE CIBA COLLECTION OF MEDICAL ILLUSTRATIONS—Volume 5—Heart (A Compilation of Paintings on the Normal and Pathologic Anatomy and Physiology, Embryology, and Diseases)—Prepared by Frank H. Netter, M.D.; Edited by Frederick F. Yonkman, M.D., Ph.D. Commissioned and published by CIBA. CIBA Pharmaceutical Company, Division of CIBA Corporation, 556 Morris Avenue, Summit, N. J. (07901), 1969. 295 pages. Copies may be ordered from the Publications Section, CIBA Pharmaceutical Company, 556 Morris Avenue, Summit, N.J. (07901), \$29.50 (sold at cost).

CIBA FOUNDATION STUDY GROUP NO. 33—ADRENERGIC NEUROTRANSMISSION (in Honour of U. S. von Euler)—Edited by G. E. W. Wolstenholme and Maeve O'Connor. Little, Brown and Company, 34 Beacon Street, Boston, Mass. (02106), 1968. 123 pages, \$4.50.

A CIBA FOUNDATION SYMPOSIUM—THE ROLE OF LEARNING IN PSYCHOTHERAPY—Edited by Ruth Porter. Little, Brown and Company, 34 Beacon Street, Boston, Mass. (02106), 1968. 340 pages, \$12.00.

THE CLINICAL APPROACH TO THE PATIENT — William L. Morgan, Jr., M.D., Professor of Medicine, The University of Rochester, School of Medicine and Dentistry; George L. Engel, M.D., Professor of Psychiatry and Professor of Medicine, The University of Rochester, School of Medicine and Dentistry; Illustrated by Evelyn Lipman Engel. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 314 pages, \$9.75.

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CONTROVERSY IN OBSTETRICS AND GYNECOLOGY—Edited by Duncan E. Reid, M.D., and T. C. Barton, M.D., Boston Hospital for Women. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 414 pages, \$15.50.

GENETICS AND COUNSELING IN MEDICAL PRACTICE—Leonard E. Reisman, M.D., Associate Professor of Pediatrics and Pathology, The Jefferson Medical College of Philadelphia; and Adam P. Matheny, Jr., Ph.D., Assistant Professor of Pediatrics and Chief Psychologist, Children and Youth Project, University of Louisville School of Medicine. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1969. 215 pages, 86 illustrations, \$12.75.

AN INTRODUCTION TO CHILD PSYCHIATRY—Second Edition—Stella Chess, M.D., Associate Professor of Psychiatry, New York University Medical Center; Associate Visiting Psychiatrist, Bellevue Hospital. Grune & Stratton, Inc., 381 Park Avenue South, New York (10016), 1969. 263 pages, \$6.75.

MANUAL FOR LABORATORY CLINICAL CHEMISTRY—Albert Hanok, M.D., Assistant Professor, Department of Biochemistry, The Bronx Municipal Hospital Center and The Albert Einstein College of Medicine. Geron-X, Inc., Box 1108, Los Altos, Ca. (94022), 1969. 441 pages, \$12.00.

THE ORGANIZATION OF MEDICAL CARE UNDER SOCIAL SECURITY—A Study Based on the Experience of Eight Countries—Milton I. Roemer, M.D., Professor of Public Health, University of California, Los Angeles. International Labor Office, Washington Branch, 917 - 15th Street, N.W., Washington, D.C. (20005), 1969. 241 pages, \$2.75 (Paperback).

ORGANIZATION AND ADMINISTRATION OF HEALTH CARE—Theory, Practice, Environment—Richard L. Durbin, A.B., M.B.A., M.P.A., Administrator, Temple University Hospital; Associate Professor, Temple University School of Business, Philadelphia; and W. Herbert Springall, A.B., M.P.H., Associate Administrator, Temple University Hospital; Assistant Professor of Hospital Administration and Chairman, Department of Health Care Management, Temple University College of Allied Health Professions, Philadelphia. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1969. 248 pages, 51 illustrations, \$9.85.

PROGRESS IN COMMUNITY MENTAL HEALTH—Volume I—Edited by Leopold Bellak, M.D., and Harvey H. Barten, M.D. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 272 pages, \$11.75.

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PROGRESS IN MEDICAL GENETICS—Volume VI—Edited by Arthur G. Steinberg, Ph.D., Professor of Biology, Department of Biology, and Associate Professor of Human Genetics, Department of Preventive Medicine, Case Western Reserve University, Cleveland, Ohio; and Alexander G. Bearn, M.D., Professor and Chairman of the Department of Medicine, Cornell University Medical College and Physician-in-Chief, The New York Hospital, New York. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 288 pages, \$16.75.

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REVIEW OF GROSS ANATOMY—Second Edition—Ben Pansky, Ph.D., M.D., Formerly Associate Professor of Anatomy, New York Medical College, Flower and Fifth Avenue Hospitals, New York, N.Y.; Earl Lawrence House, Ph.D., Professor of Anatomy, New Jersey College of Medicine and Dentistry, Jersey City, N.J. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1969. 494 pages, \$6.95.

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PREMATURITY AND THE OBSTETRICIAN—Denis Cavanagh, Professor and Chairman, Department of Gynecology and Obstetrics, Saint Louis University School of Medicine, Director of Gynecology and Obstetrics, Saint Louis City Hospital, Saint Louis, Missouri; and M. R. Talisman, Clinical Assistant Professor of Obstetrics-Gynecology, The University of Miami School of Medicine, Miami, Florida. Foreword by Arthur E. McElfresh. Appleton-Century-Crofts (Division of Meredith Publishing Company), 440 Park Ave. South, New York, N.Y. (10016), 1969. 542 pages, \$16.50.

THERAPEUTIC RADIOLOGY—Rationale, Technique, Results—Third Edition—William T. Moss, M.D., Professor of Radiology, Northwestern University School of Medicine, Department of Radiology, Chicago, Illinois; Director, Department of Therapeutic Radiology, Chicago Wesley Memorial Hospital; Chief, Department of Therapeutic Radiology, Veterans Administration Research Hospital, Chicago, Illinois; and William N. Brand, M.D., Associate in Radiology, Northwestern University School of Medicine, Department of Radiology, Chicago, Illinois; Assistant Attending Department of Therapeutic Radiology, Chicago Wesley Memorial Hospital. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1969. 564 pages, \$22.50.

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Maximal Treadmill Stress Testing for Cardiovascular Evaluation—M. H. Ellestad et al (Memorial Hosp., Long Beach, Calif.), *Circulation* 39:517-522 (April) 1969.

A maximum treadmill stress testing procedure using energy equivalents of four times basal (1.7 MPH), and 15 times basal (5 MPH) has been used in normals and cardiacs from 7 to 83 years of age. In a total of 4,028 tests there has been no mortality; 63% of those with ischemic ST segment depression failed to experience pain of any type. Continuous ECG monitoring increases safety and the diagnostic yield. Use of the maximum predicted pulse rate helps establish the optimum stress for each patient.

Some Active Derivatives of Penicillin — L. D. Brown (P.O. Box 280, Orrville, Ohio), W. A. Zygmunt, and H. E. Stavelly, *Appl. Microbiol.* 17:339-343 (March) 1969.

The antibacterial activities of a number of amide derivatives of penicillin against both penicillin-sensitive and penicillin-resistant cultures were determined. Several possessed significant inhibitory activity against certain gram-positive bacteria. The amides, although resistant to the destructive action of β -lactamase, did not protect penicillin G in competitive experiments. One derivative, the *O*-benzylhydroxamide of penicillin G, was active against six of eight penicillin-resistant strains of *Staphylococcus aureus* (minimal inhibitory concentration, 0.2 μ g/ml or less), but had only a minimal in vivo activity against mouse *Streptococcus* infections.

Low Protein Diet and Psoriasis—H. S. Zackheim and E. M. Farber (Stanford Univ. School of Medicine, Palo Alto, Calif.), *Arch. Derm.* 99:580-586 (May) 1969.

Thirteen patients with psoriasis were hospitalized for periods of 4 to 17 weeks and maintained on varying levels of protein intake ranging from 4.0 to 162 gm daily. Local therapy was restricted to a bland cream. All patients improved during the first seven weeks of hospitalization, and only two relapsed thereafter. No significant difference in the degree or rapidity of improvement on the various dietary protein levels was evident. Three patients who improved while on a low-protein intake continued to improve or failed to flare when changed to a high-protein diet. Low-protein, low-tyrosine, or low-tryptophan diets seem to be of little value in the management of psoriasis.



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New Trends in the Treatment of Angina Pectoris

DEAN T. MASON, M.D., JAMES F. SPANN, JR., M.D., AND
ROBERT ZELIS, M.D., *Davis*

■ *Traditionally when considering the pharmacologic basis of therapy in angina pectoris, attention is focussed on alterations of coronary blood flow. Yet the diseased coronary arteries in these patients often do not appear to be capable of responding to vasodilatory drugs. Since the pain of myocardial ischemia is relieved by a number of interventions without an increase in coronary blood flow, the concept herein considered is that angina pectoris is best viewed as an unfavorable relation between myocardial oxygen requirements and availability. Thus, the clinical value of the major antianginal agents is thought to be based importantly upon their actions to reduce myocardial oxygen consumption rather than to increase coronary blood flow.*

Sublingual nitroglycerin possesses a powerful dilator effect on veins which reduces venous return and thereby the size of the heart and intramyocardial tension; thus myocardial oxygen requirements are diminished.

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The introduction of electrical stimulation of the carotid sinus nerves as a means of therapy in patients with angina pectoris has provided a powerful tool for the treatment of patients with refractory ischemic pain.

IT HAS BEEN the traditional view that the relief of angina pectoris in patients with coronary arterial disease is the result of improving blood flow to the ischemic myocardium.¹⁻³ However, it has been shown that the diseased coronary arteries in patients with coronary atherosclerosis often are not capable of responding to vasodilator drugs, yet pain due to myocardial ischemia is relieved by certain antianginal agents without an increase in coronary blood flow.⁴⁻⁷ It is proposed in this discussion that angina pectoris is related to an unfavorable relation between myocardial oxygen demands and the availability of oxygen to the heart, or the ratio of myocardial oxygen consumption to coronary blood flow. Thus, angina is diminished by reducing the demands of the heart for oxygen just as it would be reduced by increasing the flow of blood to the ischemic myocardium.

It has now become established that the oxygen requirements of the heart are critically related to three hemodynamic factors (Chart 1).⁸⁻¹⁰ The main one is the intramyocardial tension that the heart must develop during contraction and is the product of the intraventricular systolic pressure and the volume of the ventricular chamber. The other two important variables directly related to myocardial oxygen requirements are the heart rate and the contractile state of the heart. Thus, the interplay of these determinants as they are influenced by certain mechanical, metabolic, neural and humoral factors determines the oxygen requirements of the heart. The central idea advanced in this treatise is that the salutary clinical benefits derived from the commonly used drugs and certain of the techniques employed in the treatment of angina pectoris—nitroglycerin, propranolol (Inderal®), and carotid sinus nerve stimulation—result to an important extent from the actions of these interventions in reducing myocardial oxygen consumption rather than in increasing coronary blood flow.

Nitroglycerin

Although the nitrites have been used in the treatment of angina pectoris for a full century,¹¹ the precise mechanism by which these agents relieve this symptom has not been defined. The nitrites

EFFECTS OF THE MAJOR ANTIANGINAL MEASURES ON THE HEMODYNAMIC DETERMINANTS OF MYOCARDIAL OXYGEN CONSUMPTION

	Nitrites	β -Block	CSN Stim.*
1. Intramyocardial Tension (intraventricular systolic pressure x ventricular volume)	↓ ↓	↓	↓ ↓
2. Heart Rate	↑	↓ ↓	↓ ↓
3. Cardiac contractility	↑	↓ ↓	↓ ↓

*Carotid sinus nerve stimulation

Chart 1.—Effects of the major antianginal measures on the hemodynamic determinants of myocardial oxygen requirements.

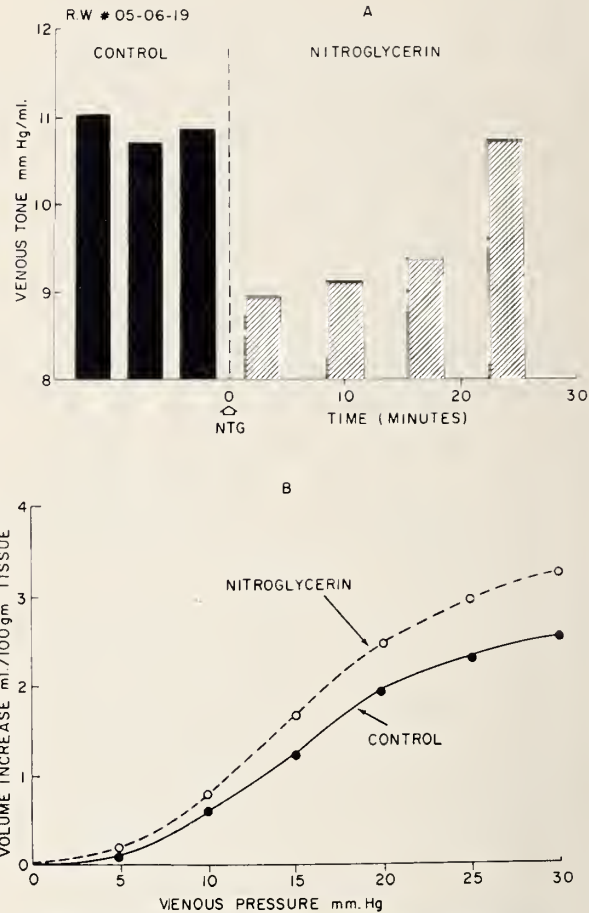


Chart 2.—A. Venous tone measurements during the control period (solid bars) and at intervals after the administration of sublingual nitroglycerin (cross-hatched bars). B. Relation between venous pressure and forearm volume increase during the control period (solid line) and after sublingual nitroglycerin (dashed line). (Reproduced by permission from Mason, D. T. and Braunwald, E., Circulation 32:755-766, Nov., 1965 (24).

From the Cardiopulmonary Section, Departments of Medicine and Physiology, University of California, Davis, School of Medicine, Davis.

Presented before a Joint Meeting of the Section on Internal Medicine and The American College of Cardiology at the 98th Annual Session of the California Medical Association, Los Angeles, March 15 to 19, 1969.

Reprint requests to: Cardiopulmonary Section, Department of Medicine, University of California, Davis, School of Medicine, Davis 95616. (Dr. Mason).

as a group are generally considered to include the inorganic nitrite ion and the organic nitrites and nitrates, each of which possesses the fundamental effect of directly relaxing smooth muscle of arterioles and veins.¹² The most important agent of this group clinically is the organic nitrate, glyceryl trinitrate (nitroglycerin). Although nitroglycerin produces coronary vasodilation in normal man, it does not regularly increase coronary flow in patients with coronary arterial disease.^{4,7}

The possibility was considered that one of the major therapeutic actions of nitroglycerin is to diminish the needs of the heart for oxygen and that this effect might be dependent upon the drug's actions on the peripheral circulation.¹³ Accordingly, the effects of this drug on the arterioles and veins of the human forearm were determined when it was administered in the manner employed in clinical practice—sublingually. These studies have shown that nitroglycerin results in a reduction in the distensibility of the venous system, or a decline in venous tone, and thereby causes pooling of blood in the peripheral veins, an action which diminishes the return of blood to the heart (Chart 2). In addition, the agent produces a mild decline in systemic arterial pressure, a concomitant elevation of forearm blood flow, and thus a decrease in calculated forearm vascular resistance.

The finding that sublingual nitroglycerin results in dilation of forearm veins and peripheral pooling of blood suggests the possibility that this drug might reduce ventricular size and intramyocardial tension and thereby reduce myocardial oxygen requirements (Chart 1). In this manner, nitroglycerin would influence the relation between the demand for and the availability of oxygen to the heart toward normal. Thus, the effects of nitroglycerin on ventricular size have been determined by means of a cineradiographic technique which permits the measurement of changes in ventricular dimensions in intact human subjects.¹⁴ Following nitroglycerin, decreases in both end-diastolic and end-systolic volumes were observed; the former effect was greater than the latter, and thereby stroke volume and cardiac output were reduced.^{14,15} Since there was a fall in arterial pressure, in cardiac output and in stroke volume, the calculated external work performed by the left ventricle was diminished. Further, since the size of the heart is related to the development of myocardial tension and oxygen consumption, the reduction of ventricular volume reduces myo-

cardial oxygen requirements, which explains at least in part the favorable effects of nitroglycerin in patients with angina pectoris. This postulation is in agreement with the fact that when nitroglycerin is administered to patients during attacks of angina pectoris, the abnormally elevated end-diastolic pressure in the left ventricular diminishes rapidly.²

The actions of sublingual nitroglycerin on the arterial bed also are important in reducing the tension developed by the ventricle and myocardial oxygen consumption. Thus, sublingual nitroglycerin causes arteriolar dilation and reduces arterial pressure; these effects reduce the systolic intraventricular pressure and lower the resistance offered to ventricular ejection, thereby allowing greater emptying of the chamber. It is concluded that the actions of nitroglycerin on the peripheral venous and arterial systems are important in the relief of angina pectoris because they reduce the needs of the heart for oxygen. Since the cardiac output and stroke volume are diminished, the action on the veins producing venous pooling is dominant over that on the arterioles.

It appears likely, therefore, that the remarkable clinical effects of nitroglycerin, of interrupting the pain of myocardial ischemia are dependent on these peripheral vascular actions, particularly in those patients in whom angina is relieved without an accompanying decrease in coronary vascular resistance^{4,7}; and that they are related to a combination of peripheral and coronary vasodilator effects in other patients in whom the affected coronary vessels and available collateral channels are capable of some dilation. Thus, although the traditional belief attributes the effectiveness of the short-acting nitrites in angina pectoris to a direct dilating action of the drugs on the coronary arterioles, it is the contention of this commentary that the nitrites produce little or no dilation of the diseased coronary vessels and that their peripheral vascular actions of reducing the preload and afterload of the ventricle, and thus reducing myocardial oxygen requirements, are often more important in relieving ischemic pain.

Propranolol (Inderal®)

It is helpful both from a clinical and pharmacologic viewpoint to separate the end-organ receptors for the sympathetic nervous system into two functional types—alpha- and beta-adrenergic receptors. In the cardiovascular system, only the

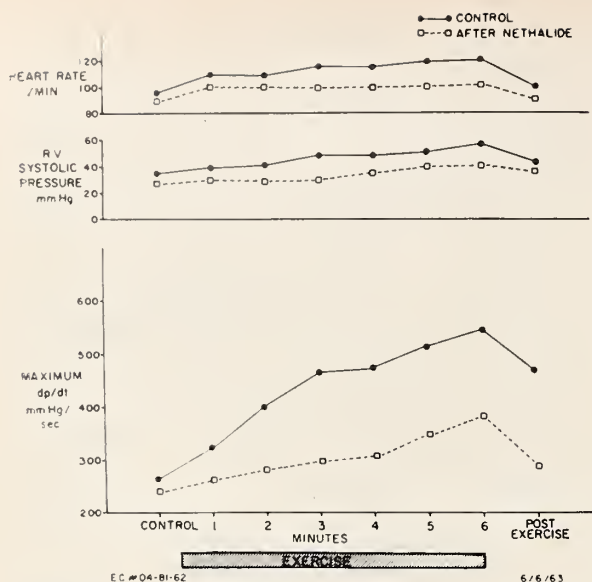


Chart 3.—The effect of exercise on heart rate, right ventricular (RV) systolic pressure, and maximum RV dp/dt (rate of pressure rise) during the control period (solid lines) and after beta-adrenergic blockade with the propranolol-like drug pronethalol (Nethalide®). (Reproduced by permission from Harrison, et al., *Circulation* 29:84-98, Jan., 1964 (17).

beta-receptors are located in the heart, while both alpha- and beta-receptors are present in the peripheral vascular beds. Activation of the alpha-adrenergic receptors results in arteriolar constriction, and stimulation of the beta-adrenergic receptors augments cardiac contractility and heart rate and produces arteriolar dilation. Drugs that antagonize these beta-adrenergic receptors have been developed only recently. The beta-receptor blocking drug now available for clinical use is propranolol, which is capable of blocking the contractile and the heart rate effects of blood-borne catecholamines and sympathetic nerve stimulation.

Propranolol is now the subject of intensive investigation for conditions in which the intensity of sympathetic drive to the heart might be excessive.¹² Since the contractility of the ventricle and the heart rate are regulated, in part, by the rate at which endogenous norepinephrine is released from sympathetic nerve endings in the heart, treatment with propranolol impairs cardiac performance during conditions such as muscular exercise in which sympathetic stimulation is one of the important adaptive mechanisms (Chart 3).^{16,17} In patients with advanced cardiac disease who are critically dependent upon increased adrenergic stimulation of the heart and peripheral blood ves-

sels for support of their failing heart, the adverse effects of propranolol on resting hemodynamics are of considerable importance.¹⁸ Thus, propranolol may precipitate heart failure in patients with advanced cardiac disease and lead to rapid progression of hypotension and dyspnea. Indeed, the drug may actually increase the oxygen needs of the myocardium by causing ventricular dilation with resultant increases in intramyocardial tension. Also, propranolol is contraindicated in patients with serious atrioventricular conduction disturbances since the agent aggravates this condition.

One of the initial clinical applications of propranolol has been the treatment of patients with angina pectoris.¹⁹⁻²³ By preventing the increase in myocardial oxygen requirements induced by the stimulation of the cardiac sympathetic nerves during exertion, propranolol has proved to be of value in many patients with angina pectoris. The mechanisms by which the drug improves exercise tolerance by delaying the onset of ischemic pain in these patients depend on the effects of the agent of reducing myocardial oxygen requirements (Chart 1). Most important in this regard are the actions of propranolol to reduce heart rate, to reduce the contractile state of the heart and to lower arterial pressure by lowering cardiac output. Thus, propranolol exerts its salutary clinical effects in patients whose exercise capacity is limited by angina due to an unfavorable relation between myocardial oxygen requirements and availability, while the drug is detrimental to patients whose activity is limited principally by an impairment of the pumping properties of the heart and resultant symptoms of cardiac failure. Thus, propranolol exchanges the property of contractility for a reduction in the oxygen requirements of the heart.

There has been the notion that drugs (such as propranolol) which diminish the heart's need for oxygen might actually be harmful in patients with coronary disease, since it has been contended that these patients might continue activity through an ischemic episode which would ordinarily produce ischemic pain and serve as a warning that activity should be discontinued. However, this is not the case during beta-blockade, since angina pectoris still occurs at the same unfavorable ratio of myocardial oxygen consumption to coronary blood flow that produced this symptom before the drug was given. What does occur is that propranolol diminishes myocardial oxygen consumption and thereby offsets the development of this

unfavorable relation in the presence of a reduced blood flow to the myocardium.

It is apparent that a combination of propranolol and nitroglycerin is potentially more beneficial than the use of either drug separately, since these two agents work by different mechanisms in diminishing the needs of the heart for oxygen. The favorable effects of nitroglycerin on the peripheral vessels are opposed to an extent by reflex activation of the sympathetic nervous system.²⁴ The beneficial direct vasodilator effects of nitroglycerin can be extended by its combination with propranolol. These comments concerning nitrites chiefly refer to the usefulness of the short-acting nitroglycerin of abolishing the acute episode. The long-acting organic nitrites for the prophylaxis of anginal attacks have generally been less effective, although recent studies have shown some synergism between isosorbide dinitrate and propranolol.^{13,25} Furthermore, there is some evidence that tolerance might develop to the therapeutically beneficial vasodilator effects of nitrites during long-term prophylaxis, and the possibility exists that cross-tolerance to the effectiveness of nitroglycerin might develop as well.^{26,27}

Carotid Sinus Nerve Stimulation

The development of the technique of electrical stimulation of the carotid sinus nerves in the treatment of refractory angina pectoris represents an important new approach to the management of angina pectoris.²⁸ This method utilizing a radio-frequency stimulator consists of surgical attachment of bipolar electrodes to both carotid sinus nerves and connecting them to a receiving unit beneath the skin of the anterior chest. On the surface above this receiver is fixed an induction coil which is attached to an externally placed battery-powered signal generator strapped about the patient's waist.

When the patient experiences angina pectoris or is confronted with an angina-producing situation, he may switch on the battery unit to stimulate the carotid sinus nerves. This stimulation leads to an increase in afferent impulse traffic to central autonomic centers and results in reflex diminution of adrenergic discharges to the entire cardiovascular system. Thus, arteriolar dilation is produced, myocardial contractility is diminished, and heart rate is slowed—all actions that result in a reduction of myocardial oxygen requirements. Since it is necessary to stimulate the carotid sinus nerves

electrically for only a brief period until angina is relieved, this decrease in contractility persists for just a short time and does not produce cardiac decompensation in patients with advanced heart disease.

From the above observations it is apparent that, of the major methods available for the treatment of angina pectoris, stimulation of the carotid sinus nerves is the most powerful means of reducing the requirements of the heart for oxygen (Chart 1). Thus, beta-adrenergic stimulation of the heart is inhibited, and thereby, negative inotropic and chronotropic effects are brought about as they are by propranolol. In addition, alpha-adrenergic receptor stimulation is reduced, which brings about arteriolar dilation. Therefore, electrical stimulation of the carotid sinus nerves not only provides a powerful combination of indirect vasodilation and propranolol-like actions on the heart but also includes a greater reduction in arterial resistance and arterial pressure than with the use of nitroglycerin and propranolol together, since opposing reflex alpha-adrenergic constrictor effects on the arterioles are inhibited. It is of interest to postulate that the use of nitroglycerin in patients employing electrical excitation of the carotid sinus nerves would be helpful if angina were not relieved by baroreceptor stimulation, since the direct vasodilator actions of the nitrites would be additive to the indirect vasodilation produced by inhibition of the activity of the sympathetic nervous system.

Thus far the method of carotid sinus nerve stimulation has been applied in only a few patients with long-standing refractory angina; in them it has been highly successful.²⁸ There is the possibility that since carotid sinus nerve stimulation allows increased physical activity in patients with severe coronary disease, formation of collateral vessels might occur and thereby favorably influence the chronic course of this disease. It should be stressed that carotid sinus nerve stimulation requires the surgical application of the electrode-stimulator unit under general anesthesia, a procedure which carries with it some risk. Implantation of the pacemaker should be offered only to patients in whom the use of nitroglycerin, propranolol and other drugs has not diminished the frequency of angina pectoris.

The relative merits of carotid sinus nerve stimulation, of implantation of the internal mammary artery into the ischemic myocardium^{29,30} and of surgical reconstruction of the coronary artery³¹ in

patients with refractory angina pectoris are not settled. It would appear, however, that in older patients with advanced heart disease in whom the risks of thoracotomy are particularly hazardous, carotid sinus nerve stimulation for symptomatic relief of angina is preferable. Perhaps the Vineberg procedure or, with segmental obstructive lesions, the aorta-to-coronary artery saphenous vein bypass graft technique, is more applicable in younger patients with coronary disease in whom improved perfusion of the myocardium and long-term rehabilitation are of special importance.

TRADE AND GENERIC NAMES OF DRUGS

<i>Inderal</i> ®	Propranolol
<i>Nethalide</i> ®	Pronethalol

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Esophageal Atresia and Tracheo-Esophageal Fistula

25 Years' Experience and Current Management

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■ *A review of the experience with esophageal atresia and tracheo-esophageal fistula over a 25-year period appears to lead to the advisability of the following procedures in surgical management:*

- *Emergency gastrostomy under local anesthesia in all patients.*
- *Extrapleural interruption of tracheo-esophageal fistula and end-to-end esophago-esophagostomy in patients who have the common type of upper esophageal atresia with distal tracheo-esophageal fistula.*
- *Upper esophageal stretching and eventual esophago-esophagostomy in patients with proximal and distal esophageal atresia with or without proximal tracheo-esophageal fistula.*

IT HAS BEEN almost 30 years since Ladd and Leven^{1,2} treated the first surviving patients who were born with esophageal atresia. In the intervening years the anesthetic management of neonates has improved significantly, the general supportive measures for the surgically treated have become more specific and effective, and various surgical approaches have been tried and either discarded or continued depending upon their effectiveness.³⁻⁶ For these reasons the overall survival of such patients now generally exceeds 50 percent and is more or less dependent upon the well known incidence of associated anomalies and the degree of prematurity. The term infant without significant congenital anomalies should survive with present management.

During the past few years, our approach to the patient with esophageal atresia and tracheo-esophageal fistula has changed in several respects. The reasons for these changes and the results will be presented in this retrospective review.

Material of Study

During the past 25 years there have been 30 patients with esophageal atresia at the White Memorial Medical Center. The first three of these patients died before receiving any definitive treatment. The remaining 27 were treated surgically. Twenty-eight of the patients had proximal esophageal atresia with distal tracheo-esophageal fistula. One had proximal and distal esophageal atresia without fistula. One had proximal esophageal atresia with fistula and distal esophageal atresia without fistula. The last mentioned patient will be discussed in detail later in this communication.

From the White Memorial Medical Center, Los Angeles.

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From 1953 to 1957 there were nine patients, with one survivor. The subsequent decade, 1958 to 1968, is divided into two five-year periods. During the first five-year period (1958 to 1963) there were 12 patients, three surviving. From 1964 to 1968 there were nine patients, with eight surviving (Table 1).

Early in the history of tracheo-esophageal fistula and esophageal atresia the high incidence of associated congenital anomalies was recognized. Fourteen infants in this series had one or more additional anomalies (Table 2). The incidence and distribution were in agreement with most reported series.^{4,5,7}

Treatment

It is well known that (1) pulmonary complications, (2) prematurity, (3) associated major congenital anomalies, and (4) anastomotic leaks are the major factors leading to death in these infants.^{3-5,7,8} The deaths in this series further emphasize the above causes of death (Table 3). The im-

portance of gastrostomy has become more widely accepted in recent years, and all patients in our care now have emergency gastrostomy under local anesthesia as soon as the diagnosis is established. The reasons are as follows: Diaphragmatic motion and pulmonary function are better after gastric decompression, endotracheal anesthesia is easier and safer, postoperative feedings can be given through the gastrostomy until the infant is vigorous enough to swallow via the esophagus, and retrograde esophageal dilation, using the Tucker dilators, is easily performed through the opening. In this series of patients there were 19 who had gastrostomy, and 11 of them survived. Of the seven who did not have gastrostomy, one survived.

Following gastrostomy, upper pouch suction is instituted with the Replogle tube connected to constant suction. In addition, members of the nursing staff perform manual pharyngeal suction frequently to protect the trachea from overflow of saliva.

Although extrapleural dissection for interruption of the tracheo-esophageal fistula and anastomosis of the esophagus requires approximately 20 minutes additional operating time, this time is well spent in comparison with the quicker transpleural approach to the trachea and esophagus. Even if a small opening is made in the pleura, it is advisable to proceed with the extrapleural dissection. There are fewer pulmonary complications with this approach but, more important, if there is an anastomotic leak this is well tolerated through the extrapleural space, but virtually a mortal insult if the esophagus leaks transpleurally. With the extrapleural approach, staging (which we formerly recommend for premature infants) is rarely indicated or necessary.⁸ The fourth rib is resected subperiosteally and the extrapleural space is approached through the bed of the fourth rib. By so doing we hope to obviate the scoliosis which has been a sequel to a vertical incision with multiple rib resections. Of 12 patients with the extrapleural dis-

TABLE 1.—Survival of 30 Infants with Tracheo-Esophageal Fistula and Esophageal Atresia

Time	Total Patients	Number Survivors	Percent
1944-57	9	1	11.0
1958-63	12	3	25.0
1964-68	9	8	88.8
25 Years	30	12	40.0

TABLE 2.—Associated Congenital Anomalies in 14 Patients with Tracheo-Esophageal Fistula and Esophageal Atresia

Anomaly	Number
Congenital Malformations of the Heart and Great Vessels	13
Genitourinary System	6
Musculoskeletal	6
Gastro Intestinal Tract	4
Respiratory	4
Mongolism	4
Miscellaneous	2

TABLE 3.—Factors Responsible for Death in 18 Patients with Tracheo-Esophageal Fistula and Esophageal Atresia

Time	Total Patients	Cause of Death	Number	Total Deaths
1944-57	9	Pulmonary Complications	6	8
		Major Congenital Anomaly	1	
		Cardiac Arrest Intraoperative	1	
1958-63	12	Pulmonary Complications	4	9
		Cardiac Arrest Intraoperative	2	
		Anastomotic Leak	2	
		Major Congenital Anomaly	1	
1964-68	9	Interstitial Pneumonia	1	1

section, eight have survived, and of 14 with the transpleural dissection four have survived.

An Unusual Sequela

In one patient with esophageal atresia, achalasia developed at age six years. It is well known that esophageal motility in patients with esophageal atresia is abnormal. Lind⁹ demonstrated that esophageal motility in patients who have had surgical correction of esophageal atresia is similar to that of achalasia in adult patients. It is somewhat puzzling, then, that more patients with esophageal atresia do not develop clinical and x-ray findings of achalasia. The patient in our series in whom achalasia did develop was one of a set of premature twins who was treated by surgical staging.¹⁰ Initially, the fistula was ligated in continuity and subsequently the esophagus was reconstructed anatomically. A recurrent tracheo-esophageal fistula developed with a rather severe esophageal stricture, requiring resection and esophageal reanastomosis. When the patient was six years old it became apparent he had achalasia (Figure 1). The time-honored Heller type myotomy¹¹ was temporarily beneficial, but achalasia recurred and the second time was treated with the Jackson-Mosher dilator, which corrected the defect.

Esophageal Atresia Without Fistula

An infant with esophageal atresia without fistula from either esophageal segment, or with fistula from the upper esophageal segment only, can be treated in a similar staged fashion. The common method of bridging the gap between the two atretic segments of the esophagus has been to interpose a segment of colon.^{3,12} This affords a satisfactory conduit for the passage of food and fluids from the mouth to the stomach, but the operation is long and somewhat difficult, and often there are serious complications. Stricture formation, anastomotic leaks, lengthening of the colonic segment and reflux of fluids into the tracheo-bronchial tree, resulting in bronchitis and pneumonia, are common ones. More recently a number of such patients have had eventual anatomic esophageal reconstruction after stretching of the upper pouch.^{13,14} In the past it was felt that in some of these patients the gap was too wide to permit end-to-end anastomosis. The majority of such patients can eventually have the advantage of an anatomical esophagus rather than interposition of



Figure 1.—Achalasia in a six-year-old twin previously operated upon for tracheo-esophageal fistula and esophageal atresia.

a colon segment. The following case illustrates the point.

Report of a Case

The patient, a baby girl weighing 6 pounds 2 ounces at birth, which was attended by hydramnios, had feeding difficulties. X-ray films

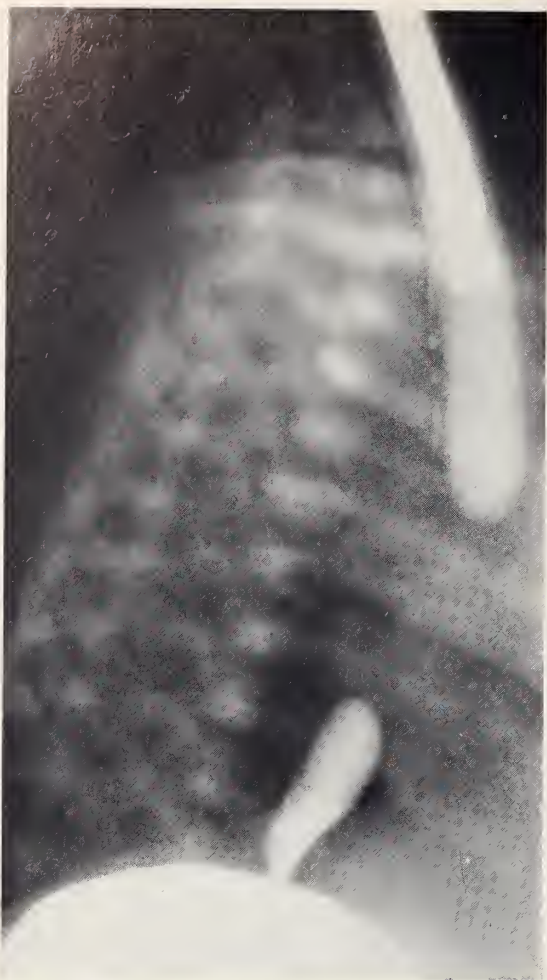


Figure 2.—Stretching of the proximal pouch, using a mercury-weighted bougie. Also seen is the distal atretic segment filled with barium.

revealed a blind upper esophageal segment and a gasless abdomen. Gastrostomy was performed under local anesthesia, after which an opaque medium introduced through the gastrostomy tube was noted to pass from the stomach into the small bowel without evidence of obstruction. (Radiographic studies of this kind are important in the treatment of such patients because, with no gas in the stomach or small bowel, one has no way of excluding the possibility of a small bowel atresia. If small bowel obstruction is present and feedings are attempted the gastrostomy is very likely to leak and peritonitis ensue.) The infant was fed through the tube, and suction was applied to the upper esophageal segment, which was stretched daily with a mercury-weighted bougie (Figure 2). This lengthened the segment, which was 11 cm from the gum line to the distal end at birth, to

14 cm at ten weeks of age. Esophago-esophagostomy was then performed by extrapleural dissection through the bed of the fifth rib. An unanticipated finding was a side fistula between the upper esophagus and the trachea. This defect was closed. Although the distal esophagus also was short, by mobilizing the upper esophagus and the distal esophagus it was possible to bring the two esophageal segments together under moderate tension with two layers of interrupted silk. Postoperatively the anastomotic junction leaked, but this was tolerated by the infant and eventually it closed spontaneously. An esophageal stricture that ensued was overcome by repeated dilation with Tucker dilators. At 10 months of age the patient weighed 16 pounds 1¾ ounces. She required occasional esophageal dilations and was eating food appropriate for her age.

Comment: The unusually wide gap between the esophageal segments in this patient—more than 3 cm at birth—would suggest that, since esophageal anastomosis was successful in this patient the majority of such patients can have an anatomical esophagus with its inherent advantages.

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The Potentially Suicidal Patient

Detection and Management in Office Practice

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IN THE UNITED STATES TODAY suicide is the tenth major cause of death. Each year about 20,000 people kill themselves. The actual rate, including victims who conceal a suicidal death or self-inflict death "by accident," may approach 50,000. About 60 percent of suicides have history of previous attempts and 10 percent of those who attempt suicide and survive kill themselves later. It is estimated that for every person who kills himself there are at least ten others who attempt and fail.¹ About half of all who kill themselves see a physician sometime during the month before. And most physicians see about six potentially suicidal patients each year, but rarely is the chief complaint elicited during the office visit, "I'm thinking of killing myself."

The signs of potential suicide are unfortunately very "soft." Even if they are aware of the signs, few busy clinicians view potential suicide as a killer to be ruled out in their long list of differential diagnosis. Yet tuberculosis, the twentieth greatest killer in this country,² and twelfth worldwide, is frequently considered in differentiation. How can the physician, faced with imposing statistics that convey the waste of human resources through suicide, better detect and manage the suicidal patient in office practice?

Suicidologists have devised a sophisticated Suicide Potential Rating Scale (SPRS) which provides a degree of reliability in assessing the suicidal potential of a given patient.* The depression scale of

the Minnesota Multiphasic Personality Inventory (MMPI) is thought by some to provide the physician with an index of suspicion about the suicidal potential of some patients.† Although both the SPRS and the MMPI are instruments of value, they are used primarily by psychologists and psychiatrists or by physicians who have greater than usual interest in establishing a laboratory-like basis for treating the emotional aspects of illness. In other words, the busy clinician would use neither instrument frequently enough to warrant training in the use of the scales. As computerized record-keeping and information retrieval systems become more readily available to groups of individual physicians, these instruments or their refinements will be of immense value.

The MMPI is currently computerized for immediate use.‡ But until more physicians are ready to supplement clinical skill with computer-processed information, most of us will continue to assess suicidal risk wholly by means of clinical interview. To do this well, we must become acquainted with the varieties of suicidal behavior of individual patients.

This requires developing a little more patience than we often have, mastering more anxiety than we are often aware of, and, most important, believing that our responsibility in delaying death is not limited to diseases amenable to treatment by drugs and instruments. We need more patience because uncovering and evaluating suicidal thoughts can be a slow and circuitous process. We need to master our own anxiety because we physicians are

*Suicide Prevention Center Assessment of Suicidal Potentiality Form. Suicide Prevention Center, 2521 W. Pico Boulevard, Los Angeles, California 90061.

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Reprint requests to: Department of Psychiatry, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033.

†Minnesota Multiphasic Personality Inventory. Psychological Corporation, 304 East 45th Street, New York, New York 10017.

‡Roche Computerized Form of MMPI, Roche Psychiatric Service Institute, Box 170, Newark, New Jersey 07101.

not often comfortable with situations that challenge our effectiveness outside of our conventional roles. And we need take more responsibility because those of us who view suicide as a problem of theology, philosophy or personal conscience and not medicine, will probably convey such a view to the patient who seeks help. The physician aware of these requirements can do much to detect and manage a potentially suicidal patient.

The Potentially Suicidal Patient

The New Patient

When any patient appears for the first time in a physician's office for routine examination or with a myriad of vague complaints, the medical work-up should include an assessment of how the patient has dealt with stress in the past. This does not have to be done on the first visit, but if the physician's concern is aroused by factors which we will soon discuss, it is better to make the assessment as early as possible. For example, if after loss of a job, loss of a loved one, or loss of self-esteem, the patient's mourning, despair or apathy persisted with little relief for longer than six to twelve weeks,³ the physician should re-explore the vague somatic complaints elicited in the patient's description of his

present illness or in the systems review. If anxiety, weight loss, insomnia, fatigue, social withdrawal, and waning interest lingered long after the loss, the physician should determine whether this is characteristic of the patient's reaction to stress or whether it represents a newly emerging pattern of behavior.

Characteristic Reaction to Stress

If the physician infers that the behavior is of an old established pattern with this particular patient, he should tactfully explore past suicidal potential by honestly asking the patient how he overcame the specific stresses and whether he continues to dwell over them now. If the patient appears more uncomfortable at this point, the physician can gently, but matter-of-factly, confront the patient with his seeming discomfort. This confrontation may demonstrate to the patient that the physician can understand and discuss such discomfort.

If the patient denies past conflict or current discomfort, the physician can honestly state that as part of a thorough medical evaluation he wishes to know if the patient ever thought about suicide. Asking him does not plant the seeds of suicidal thoughts. In most cases, the character of the response will allow the physician to determine its

TABLE 1.—*Suicide Rate Per 1,000 Population Among 3,800 Suicides, by High- and Low-Risk Categories of Risk-Related Factors (reported by Tuckman and Youngman)*

Factor	High-Risk Category	Suicide Rate	Low-Risk Category	Suicide Rate
Age	45 yrs. and older	24.0	Under 45 yrs. of age	9.4
Sex	Male	19.9	Female	9.2
Race	White	14.3	Nonwhite	8.7
Marital status	Separated, divorced, widowed	12.5	Single, married	8.6
Living arrangements	Alone	48.4	With others	10.1
Employment status*	Unemployed, retired	16.8	Employed†	14.3
Physical health	Poor (acute or chronic condition in the six month period preceding the attempt)	14.0	Good†	12.4
Mental condition	Nervous or mental disorder, mood or behavioral symptoms including alcoholism	19.1	Presumably normal, including brief situational reactions†	7.2
Medical care (within 6 months)	Yes	16.4	No†	10.8
Method	Hanging, firearms, jumping, drowning	28.4	Cutting or piercing, gas or carbon monoxide, poison, combination of other methods, other	12.0
Season	Warm months (April-September)	14.2	Cold months (October-March)	10.9
Time of day	6:00 A.M. to 5:59 P.M.	15.1	6:00 P.M. to 5:59 A.M.	10.5
Where attempt was made	Own or someone else's home	14.3	Other type premises, out-of-doors	11.9
Time interval between attempt and discovery	Almost immediately, reported by person making attempt	10.9	Later	7.2
Intent to kill (self-report)	No†	14.5	Yes	8.5
Suicide Note	Yes	16.7	No†	12.3
Previous attempt or threat	Yes	25.2	No†	11.0

*Does not include housewives and students.

†Includes cases for which information on this factor was not given in the police report.

sincerity. If the patient's response is of genuine surprise or disbelief (accompanied with an "of course not!"), the index of suspicion is more often than not minimal, and the astute clinician can feel somewhat safer about this person's future suicidal risk. If the reaction is tenuous, guarded, with a change in voice, accompanied by an "I've never had the guts" response, the doctor's suspicion is obviously greater. It must be borne in mind, however, that with few exceptions a patient will relate quite honestly more profound suicidal feelings once the physician emphatically lets him know that they can be discussed. At this point some of the specific incidents in the patient's past might be discussed along with the suicidal ideas and feelings that accompanied those events.⁴

If the patient is found to have a past history of suicide attempts, the risk-related factors in suicides reflected in data reported by Tuckman and Youngman⁵ (Table 1) are of special value. This may help the physician assess high and low risk related factors in his patient's history and clinical evaluation.

When it is apparent that a patient has considered suicide in the past, the following six areas of assessing future suicidal potential should be explored with him:

1. The frequency and extent of suicidal ideas.
2. The considered means of suicide accompanying the ideas.
3. The feelings associated with the means of suicide.
4. The available means by which the idea can be acted upon.
5. The feelings of suicide accompanying ordinary acts of everyday life.
6. The ability to project how loved ones would be affected by the patient's death.

The Frequency and Extent of Suicidal Ideas

If the patient relates a series of stressful situations, most of which were accompanied by frequent suicidal thoughts, recurring many evenings when he retired and persisting when he awoke most mornings, the physician should be more alert to the potential risk of suicide.

The Considered Means of Suicide Accompanying the Ideas

On the basis of the patient's extensive past suicidal thoughts, the physician should explore the means of suicide that the patient considered. This

should be done by simply asking him, "How did you think of doing it?" This is particularly important if the patient has a family history of suicide or is profoundly depressed; if he is an alcoholic; if he is male, white, divorced, young, or over 65; if he is Protestant, unemployed, poor and if he has a chronic, long-standing but not necessarily disabling or debilitating disease. In other words, the physician's index of suspicion about a potential suicide increases as known factors of increasing suicidal risk accumulate in the patient's life history.⁶ The potential is greater (with qualified exceptions) if the patient replies, "With a gun," than if he says he had considered pills or poison. Usually the suicidal potential can be considered greater if the fantasy of suicide was bizarre or violent.

The Feelings Associated With the Means of Suicide

If the patient relates particular means by which he thought of killing himself, the physician should explore the feelings accompanying those past thoughts. If the patient speaks of having been relieved by ideas of death rather than frightened or awed by them, the potential is again great. If he discloses having had overwhelming feelings or urges to use the gun or take the pills, and of willfully fighting these feelings to avoid actually obtaining the means, the potential is great. If he does not spontaneously discuss such items, the physician should ask, "Were you relieved or frightened at the thought of using the gun on yourself at those times? How intense were the feelings of wanting to use it? Did you have to literally leave what you were doing and do something else to avoid the feelings and thoughts?" If any of these questions are answered "Yes," the patient's suicidal potential is greater than usual. Since most formerly suicidally contemplative people rarely forget the profound intensity of such feelings, an "I don't remember" answer should be viewed with suspicion. If the questions are readily negated by the patient, the suicidal potential is lessened.

The Available Means by Which The Idea Can be Acted Upon

Clinically evaluating potential risk can be aided by an exploration of what actual means are readily available to the patient to carry out his suicidal thoughts. If in his suicidal fantasy a gunsmith elaborates upon the kind of shot, the size of the bore and the position of the gun, the past risk and

the potential are obviously serious. If a ruminative physician-patient with a drinking problem scoffs at the idea of an overdose of meprobamate because it would not do the job, but has had to avoid carrying vials of sodium luminal in his bag because of the synergistic activity of barbiturates and alcohol, one has reason to consider him a high risk patient. If a housewife's recurrent fantasy was of taking the 30 tablets or capsules of a sedative she had actually hidden under the mattress, one becomes concerned. Generally speaking, the risk of potential suicide increases to the extent to which the fantasied route of suicide is actually available in the patient's environment.

Feelings of Suicide Accompanying Ordinary Acts of Everyday Life

If the patient has been using a particular freeway exit for years, and, following a stressful event, entertained recurrent thoughts and desires to speed into the abutment, the risk is great. If a patient who for years had bathed while listening to a radio on a shelf above the bathtub, has recurrent urges to nudge the radio off the shelf, his potential for suicide is very great. If a housewife is increasingly preoccupied with placing her head in a gas oven which she had used for years without such thoughts, her suicidal potential is increased. In this area of assessment, one must be careful not to confuse the obsessional patient with the one whose feelings accompany the thoughts of suicide. It is the latter category that represents high risk. The obsessive patient, who may usually be recognized by his fastidiousness, may have recurrent thoughts of suicide or violence, but they are not usually accompanied by intense feelings. When such feelings accompany the thoughts, the compulsion to act can become more overwhelming and decidedly increase suicidal risk.

The Ability to Project How Loved Ones Would be Affected by the Patient's Death

It is important that the physician determine whether the patient has considered what his death would solve, how his loved ones would be affected, and who would carry on in his absence. If such considerations are strong deterrents, the patient's chances are good for overcoming suicidal feelings should they occur. Often the patient's need for immediate relief from the suicidal crisis obscures his ability to consider the welfare of those who would be affected by his death. When dealing with the currently suicidal patient, it is extremely important

to stress this particular area of investigation. If he truly believes others would be significantly better off without him, that economic insecurity will be relieved by the benefits his death may provide and that his death solves a current stress, the potential suicidal risk is great.

Changing Reactions to Stress in a Patient Familiar to the Physician

The same criteria for suicidal potential apply to the person who is considering suicide for the first time. In most instances, the potential is less since it has not been a characteristic pattern of reacting to stress.⁷ However, the patient's current emotional resources, the effectiveness of past means of coping with stress, and the frequency of factors increasing suicidal risk must be carefully evaluated. The physician cannot dismiss a patient whom he has known for many years and who he thinks is "stable," with a reassuring comment such as "I know you would never kill yourself." The same exploration of the extent and frequency of suicidal fantasies, fantasied means, intensity of feelings, available means, and the feelings accompanying everyday acts must be undertaken. Of special leverage to the physician in dealing with a patient he has known many years is the rapport of a long-term relationship, the knowledge of the patient's past effectiveness in handling stress, and the relationship of the patient to his family and job. An exploration of these areas very early, at the first signs of behavioral change, will be of far more benefit than the medication prescribed for vague somatic complaints with little organic basis.

Most physicians feel that an early assessment of suicidal potential will frighten the patient, cause him to view the medical interview as a "psychiatric" one, and to interpret the implications of the physician's concern as an intrusion. Nothing could be further from the feelings of someone who is weighing suicide as a solution to conflict. The ambivalent suicide-prone patient is immensely relieved to know that someone is available with whom to discuss the conflict. And the need to discuss it may be the overriding motivation behind the patient's office visit. This is not to suggest that the physician ask every patient during a routine examination whether he is currently or has in the past contemplated suicide, but only those whose life styles or current conflicts, considered with the clinical manifestations, indicate more exaggerated reactions to stress.

The Currently Suicidal Patient

Once the physician's suspicion is aroused, confirmed by the explanation of the patient's suicidal fantasies, and ambivalently acknowledged by a more relieved patient, the physician must determine where the patient fits among the following types of suicidal behavior⁸:

1. Transient ideas of death.
2. Sustained ideas and recurrent wishes of death.
3. Frustrated feelings and impulsive behavior.
4. The court of last resort.
5. The logical decision to die.

Transient Ideas of Death

This is the behavior characterized in Tom Sawyer's watching his own funeral. He mourns for himself and relishes the loss suffered by those who love him. This is a "they'll love me when I'm gone" type of fantasy experienced at some time by all of us and rarely indicative of significant suicidal risk. But in an emotionally unstable person the frequency of the transient death fantasy along with previously noted high risk factors should increase the physician's suspicion. And if the patient is an adolescent, the frequency is of special concern. Suicide is the third greatest cause of death among teen-agers. Teen-agers, like Tom Sawyer, are susceptible to transient ideas of death. And although few adults believe it after reading today's headlines, youngsters in an adult world have rather limited means of coping with loss or disappointment.⁹

Sustained Ideas and Recurrent Wishes of Death

This is the type of behavior which may be established some time after the patient experiences increasing transient fantasies of death. The development of this pattern can be better understood by likening it to evoking the pain of a toothache by pressing one's tongue against the tooth. The very act which induces pain seems to relieve or master the anxiety of pain by continually calling it into play. The act, tongue against tooth, can be viewed as a habit or characteristic style learned by the patient to cope with recurrent anxiety. That finds a parallel in the patient who moves from the transient death fantasy to the more sustained idea and recurrent wish of death. He has developed, one may say, a painful habit that permits him to relieve or master the anxiety of actual or anticipated stressful situations. The patient may shift back and

forth from this behavioral type to the preceding one. And he can manipulate, often unwittingly, his environment or significant people in it by communicating his suicidal preoccupation. Here may be the patient who threatens suicide in a "non-serious" manner. But one cannot predict low risk on the basis of suicidal threat without attempt. The patient may readily slide into the next category of behavior but, before doing so, undergo a series of "furtive attempts." He may superficially cut his wrists in a futile effort to bleed. He may take a drug in less than lethal dose and find himself awake hours later. But, again, in crescendo with the previously noted risk factors, he may line up the pills, take them one at a time, and as his confusion increases, take one too many and die quite "by accident." Or, anticipating that someone will heed his "cry for help," he may miscalculate the whereabouts of a significant other person.

Frustrated Feelings and Impulsive Behavior

The suicidal potential in this form of suicidal behavior is even greater. The patient who feels he has "had it up to here" falls into this category. He sees little hope for support from his environment; he has supposedly exhausted most forms of relief and he feels frustrated and closer to anger than he would in the other forms of suicidal behavior. It has been theorized that such a person may turn upon himself the anger he feels toward others. It is this patient who runs the danger of the homicidal-suicidal act, and it is necessary for the physician to determine the degree of anger felt by the patient toward others. There is little data from which to predict the potential for both homicide and suicide, but the homicidal-suicidal pattern occurs more frequently among men than women.¹⁰ Timely intervention with such a patient can be life-saving. By offering a means through which the patient can turn his rage into words, the physician helps him minimize the immediate impulse to act.

The Court of Last Resort

The patient who feels he has exhausted all emotional resources but has survived the anger and frustration of the previously discussed behavior may turn to a pattern that can be called a "court of last resort" attitude. His suicidal potential remains high since his rage, frustration, and despair are resolved, and he vows never to experience them again. His motivation to act is generally higher because he feels better. So at the slightest

suggestion of stress, he would rather die than experience again the anguish of meeting it. This is the patient who may be within the "three-month danger period" following a prolonged depression. So the physician must be alert to the very high potential risk in the patient who has survived the rage of the preceding type of suicidal behavior. The physician cannot be lulled into complacency by the patient's apparent well-being. If he provides the patient with sleeping medication because the suicidal preoccupation apparently has passed, he risks giving him a more effective means of acting suicidally should he become less ambivalent. The "court of last resort" type of suicidal behavior perhaps results in the most deaths, topped only by the previously described "frustrated feelings and impulsive behavior."

The Logical Decision to Die

Some patients may view death as the logical solution to a current conflict. Patients of either sex, over 65 years of age, who have suffered loss of loved ones, who have chronic disease or terminal illness, fall into this category. A large proportion of physician suicides may be of the "logical decision" order, although not apparently so in life since signs and symptoms of conflict are frequently masked or denied. The college student who philosophically arrives at death as an inevitability "so why not now?" can be seen in this form of suicidal behavior. Many patients of this category, when they do see a physician, may impart their torment to him only through physical symptoms. And it is difficult to identify the very high risk patient in this category simply from clinical signs. Here, especially, one has to consider the interplay of factors such as age, sex, occupation, marital status and many others. Fortunately, although this is the highest risk category of suicidal behavior, few people fall within it.

Management of the High Risk Patient

When the physician is concerned about suicidal risk in a patient he knows, he should always consider suicidal portent within the differential diagnosis if, during an office visit, the patient has exaggerated reactions to stress or complains of vague, non-specific symptoms. At the time of stress, management entails an honest evaluation of the problem, as outlined in earlier paragraphs of this communication. The physician should tell the patient of his concern over the suicidal implica-

tions and emphasize the necessity of a return office visit.

Most physicians feel they do not have the time or the skill to cope with such a patient. However, elaborate though the detection process described in the early part of this presentation may seem, it should add no more than 15 minutes to a routine or initial office examination — certainly not too much extra to allot to new patients or to the half-dozen potentially suicidal who might be seen in a year. As for skill, a physician who bears in mind that the suicidal patient needs a non-judgmental, caring person with whom to discuss his immediate feelings and not necessarily a psychiatrist to ascertain the ultimate "cause" of these feelings, can do much to help the patient dissipate his self-destructive tendencies.

The follow-up visit need be no longer than 15 or 20 minutes. It should be scheduled by the physician while the patient is in the office. The physician should firmly establish that he is concerned with the patient's problem by instructing his secretary, in the patient's presence, to "schedule Mr. Jones from 3:30 to 3:50 Wednesday afternoon in my consultation room." Such direct instruction to the secretary personalizes the physician's attitude and temporarily divests the patient of any indignity he may feel. It also tells him the length of time allotted for discussion of his conflict, which makes it easier for the physician to end the follow-up visit.

If the suicidal risk is very grave, the physician will obviously wish to see the patient within a few days, but if the risk appears to be relatively low, the patient can be seen 20 minutes a week for six weeks, that being the usual duration of emotional crisis or reaction to loss. Fewer than six visits will suffice in some cases; often it will be necessary to see the patient over a longer period.

Listening, and Getting the Patient to Talk

To communicate with the patient, first of all one must listen. Often without much prompting the patient will tell the physician what he needs to know for the assessment of risk. When it is necessary to intervene with a silent patient the physician should matter-of-factly and empathically call attention to the non-verbal clues the patient communicates. For example, "You seem to sit much lower in that chair today," or, "You're really going to town on that cigarette." Confronting the patient with the non-verbal way in which he communicates

his feelings permits him to see the physician as someone he may discuss these feelings with. The skill here is obviously in the art of medicine and requires that the physician "read" the patient in such a way as to minimize the risk that the doctor's remarks will be misperceived as an accusation. If they are misperceived, however, the physician has an opportunity to gently wonder aloud whether the patient may not be grouping him along with everything else that is bad in the patient's world. In other words, intervention should be for the purpose of encouraging productive ventilation on the part of the patient. But the physician cannot remain inactive with the potentially suicidal patient.

After five or ten minutes of such ventilation, the physician must re-explore suicidal preoccupations the patient has had since the last visit. Exploration of the stressful situation preceding the suicidal thoughts should be resumed. Special concern should be paid to the extent to which the patient's feelings associated with the means of suicide have changed. If he has a stronger feeling about killing himself by means of a readily available weapon or drug, one's concern is heightened. In such a situation the physician might wonder with the patient whether a family member should be apprised of the seriousness of the patient's condition. In most cases, the patient who appears relieved at such a suggestion is prognostically better off than one who discourages it. For the patient who can effectively fall back on the emotional resources of family or friends, the suicidal risk is reduced. If the patient refuses to involve his family, however, the physician can convey his persistent concern to the patient by asking him if he would object to the physician's discussing the patient's difficulty with a psychiatric colleague — this rather than a direct suggestion of psychiatric consultation. Such an intervention minimizes feelings of rejection and further loss that the high risk patient may experience at the suggestion that he see someone else.

The physician's tact and concern can establish for the patient a relationship by which he can find his way back to a life he is not sure he wants. The visit should end with the physician pointing out areas in which the patient seems to be finding his way back. If the patient's feelings have diminished in intensity, or if he has, say, disposed of a supply of a lethal drug, the physician should carefully reinforce such behavior.¹¹ A remark as simple as, "Getting rid of the pills is more than you could do last week," is often of value. Any indications that

the patient has made efforts toward socialization, or that his appetite or sleeping patterns have improved or that he is brooding less are a sign of decreasing risk and should be emphasized at the end of the office visit.

The time between visits is obviously crucial to the high risk patient. At each visit the physician should reassure the patient—and not falsely—that at any time of frightening suicidal thoughts or feelings, the physician is available by phone. Some physicians may view this suggestion as an open invitation to many sleepless nights. It can be, but in most cases the patient does not exploit this privilege within the relationship. Often the very fact that the patient knows he can call diminishes the intensity of his suicidal feelings.¹²

Drug Therapy

As was previously noted, depression is not among the clinical characteristics of one of the higher risk categories of suicide-potential behavior. However, when depression is clinically evident (especially in a non-schizophrenic patient with long history of intermittent depression and little evidence of a stress-precipitating event within the preceding two or three months) a trial of imipramine, 150 to 250 mg a day for three weeks, is indicated. The advantages of using "faster-acting" desmethyl derivatives of imipramine or amitriptyline are still equivocal. The same may be said of dextroamphetamines. Sometimes a suicidally depressed patient may respond in less than three weeks, but so will some who take no antidepressants. If there is little evidence of decreased depression after three weeks of adequate dosage of imipramine (and in the absence of excessive side effects) it should be discontinued and, after a two-week interval, a monoamine oxidase inhibitor may be tried. (There are reports from England indicating that monoamine oxidase inhibitors and imipramine may be used synergistically for more effective antidepressant action, but in the pharmaceutical literature in this country the combination is associated with adverse side effects and fatalities.) Even if the depression is alleviated by use of the drugs, one must still bear in mind that the suicidal risk is not necessarily minimized thereby, as the three-month post-depression danger period is still to be considered.

The question of drugs to induce sleep in a suicidal patient is always a difficult one.¹³ The physician is often convinced that a good night's sleep

would strengthen a patient's will to live. Yet recent studies¹⁴ suggest that sleeping medications, although extending the period of sleep, may decrease dreaming which is looked upon as psychologically necessary. Nevertheless, a widely tolerated sleeping medication (prescribed in small quantities to discourage "hoarding" for a suicide attempt) can be helpful. The lethal range of barbiturates is variable, and they react quite synergistically with alcohol and neuroleptic agents. Chloral hydrate remains the safest sleeping medication. When more potent ones appear necessary for a high risk patient, the physician should caution the family as to their use and danger and arrange for a family member to dispense the medication. If this arrangement cannot be made, psychiatric consultation and putting the patient into a hospital for immediate crisis may be necessary. In any event, if over a period of six or more visits the patient's suicidal potential becomes greater, or if the physician's anxiety is heightened and his patience exhausted, psychiatric consultation is indicated, but this should be rare.

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CYSTOPERINEAL FISTULA

How would you treat a male who developed a cystoperineal fistula following abdominoperineal resection for rectal cancer?

"I would do my complete urologic investigation; I would want to double check where the fistula was in the bladder; and here it would probably be in the trigone or even more likely in the urethra. I would double-double check that by chance the ureter had not been severed, and that the outflow of urine was not from an unrecognized ureteral injury. Having done all that and assuming that it would be between the urethra or the trigone, I believe that I would just go in and cut it out and sew it up.

"I might try to do it through a perineal approach for the obvious reason that the perineal approach gives you pretty good visualization if it's 'way low down. I would not be reluctant to do it transvesically. I believe on one or two occasions under such circumstances we have done both above and below. I would certainly divert the urine by an appropriate cystostomy. I would try to use very meticulous, fastidious technique as I tried to close the fistula, and I think I would have a fair chance of doing it."

—HARRY M. SPENCE, M.D., Dallas

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CASE REPORTS

Gastrojejunal Mucosal Prolapse After Subtotal Gastrectomy

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ALTHOUGH GASTROJEJUNAL mucosal prolapse is an infrequent complication of subtotal gastrectomy, when it does occur it may cause distressing symptoms. Since anastomotic revision may relieve these symptoms, recognition of this prolapse is important. Kirklin,¹ in 1935, mentioned such prolapse and a fairly large series was reported in 1963 by LeVine et al.² That the diagnostic features are still not appreciated was brought to our attention at a refresher course when a specimen case was diagnosed correctly by only a few of those attending.

Within the last year we have observed two cases in which patients with gastrojejunal mucosal prolapse benefited from surgical revision. Classic roentgenographic features were demonstrated in both, and in one we were able to observe the development of the prolapse.

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Submitted 11 April 1969.

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Reports of Cases

Case 1. A 48-year-old man had subtotal gastrectomy and antecolic gastrojejunostomy of Hofmeister type in 1954. This was done because of intractable pain secondary to chronic duodenal ulcer. During the next 13 years the patient was in hospital several times with the diagnosis of acute gastritis and pancreatitis.

Roentgenographic studies on several occasions over a period of four years after the operation were unremarkable. Then, in 1958, a condition that later was found to be prolapsis appeared, but it was erroneously interpreted as an extrinsic mass, and this impression continued in numerous examinations until 1967.

In 1967, the patient complained of vomiting an hour and a half after even small meals. No evidence of gastrointestinal bleeding was present. A roentgenographic diagnosis was made of prolapsed gastric mucosa associated with intermittent stomal obstruction. Comparison with the 1958 film showed the extent of prolapse had doubled in the interval. Fluoroscopic observations at the time prolapse was diagnosed in 1967 were most striking. The gastric pouch would accept about 400 ml of liquid barium. Emptying in the upright position was greatly delayed, with only small amounts of contrast material passing from the pouch into the small bowel at any one time. As the small bowel filled, the large prolapsed mass of the gastric mucosa was visible. (See Figure 1.)

The redundant gastric mucosa was excised and the histologic report described extensive hyperplasia of the gastric glandular epithelium. There was extensive edema and moderate lymphocytic and plasmocytic infiltration throughout. The final diagnosis was benign polypoid hyperplasia of the gastric mucosa.

At last report in mid-1969, the patient no longer had symptoms of gastric outlet obstruction. However he had symptoms related to "dumping," characterized by postprandial weakness and diarrhea. His weight was stable.

Case 2. A 53-year-old man had subtotal gastrectomy with gastrojejunostomy of Hofmeister type in 1963 for intractable pain associated with

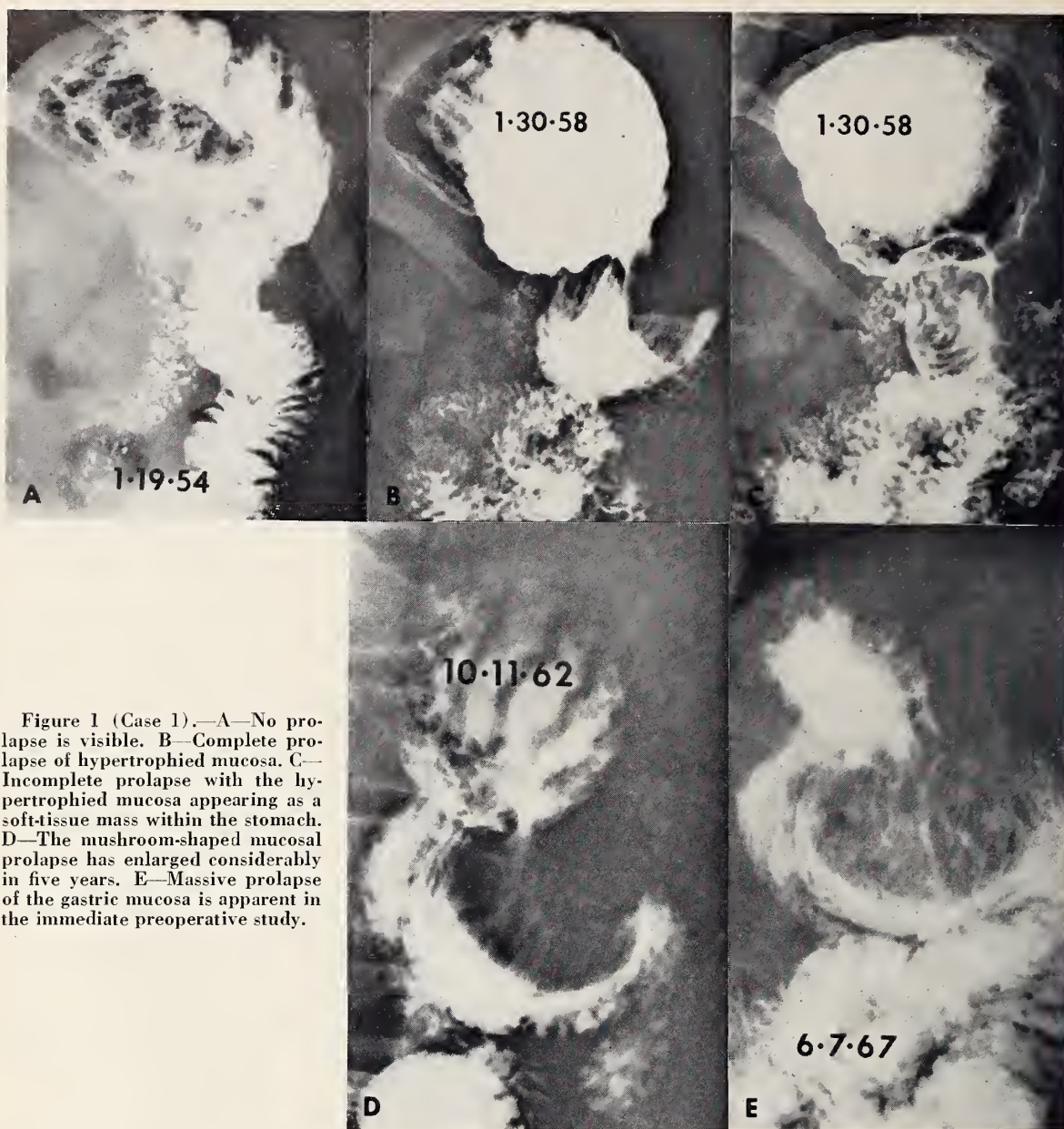


Figure 1 (Case 1).—A—No prolapse is visible. B—Complete prolapse of hypertrophied mucosa. C—Incomplete prolapse with the hypertrophied mucosa appearing as a soft-tissue mass within the stomach. D—The mushroom-shaped mucosal prolapse has enlarged considerably in five years. E—Massive prolapse of the gastric mucosa is apparent in the immediate preoperative study.

long-standing peptic ulcer. The patient had progressed well until the middle of 1967 when anorexia, nausea, weakness and dizzy spells appeared. He vomited occasionally, usually after a heavy meal. He had lost 20 pounds in the four months before admission. There was no evidence of gastrointestinal bleeding. Prolapse of gastric mucosa was diagnosed roentgenographically (Figure 2) and the redundant tissue was excised. The pathologic changes were similar to those of Case 1. After the operation the patient began to regain weight. Anorexia and weakness disappeared. When last observed, in March 1969, the patient was entirely asymptomatic.

Only a single postoperative roentgen examination was carried out following the original gastric operation. It showed the large mass at the anastomotic area to prolapse into the jejunum (Figure 2). The fluoroscopist did not observe any obstruction to the flow of barium from the stomach to the jejunum.

Discussion

In both the cases here reported, the symptoms of weight loss, nausea and vomiting after meals pointed to an obstructive process. Delayed gastric emptying, which was secondary to stomal obstruction by prolapsed mucosa, was demon-



Figure 2 (Case 2).—Prolapsed gastric mucosa is seen as a mass just distal to the stoma within the jejunum.

strated fluoroscopically in Case 1. It would seem logical that obstruction would be increased, depending upon the volume and nature of the preceding meal. Surgical revision of the anastomosis with removal of the obstructive prolapsing mucosa resulted in prompt relief of symptoms in both patients.

In the series reported by LeVine and coworkers,² bleeding occurred in six of fourteen patients. In one case the mucosal prolapse was proved to be the site of hemorrhage.

Although the afferent loop syndrome has not yet been observed with this condition, a severe enough prolapsed mucosal mass might well cause it in some patients. We must also emphasize that milder cases of prolapse, apparently entirely asymptomatic (Figure 3), have been observed by us as well as by others.²

The roentgenographic appearance of prolapse

of the gastrojejunal mucosa is ordinarily quite characteristic. Within the stomach, the gastric folds at the stoma may be somewhat stretched. The stoma may or may not be partially obstructed. The prolapsed mass is not clearly seen until after the jejunum fills and outlines the inferior rim. Peristaltic contractions of the jejunum alter the appearance of the mass. Peristalsis tugs on the mass in an attempt to propel it distally and then releases it, allowing the mass to retract toward the stomach. The mass may retract completely into the gastric pouch, and this possibility must be transmitted to the surgeon. In one of the cases reported herein, jejunotomy was done and no abnormality was seen until tilting of the operating table caused the redundant tissue to sag.

In our patients and in those previously illustrated, the prolapse appeared to be fairly symmetric. In distinguishing the prolapse from an extrinsic mass, all projections must show the mass to be intraluminal and surrounded by the circular folds of the jejunum.

The differential diagnosis would include the following considerations:

- Jejunogastric intussusception is the opposite situation and the mass with the characteristic jejunal folds is found in the gastric pouch.³ When the intussusception is reduced, the jejunum appears normal.
- A more serious problem is that of neoplasm at the anastomotic junction, which would be particularly troublesome had the subtotal resection been done for gastric cancer.

While no radiologic features such as lack of distensibility or flexibility of the residual pouch were observed in the present cases, gastric cytologic examination was conducted before operation, as the surgeons were aware that a malignant tumor was a possibility. In both cases the results of cytologic studies were negative.

The only experimental evidence to support an etiologic agent is that reported by LeVine and coworkers,² who reproduced the roentgenographic appearance in a dog. The investigators created a gastrojejunal anastomosis by dissecting out a 2-inch mucosal cuff, which was folded back on itself as for colostomy stomas. They theorized that because of its smaller stoma the Hofmeister anastomosis was more likely to prolapse than was the Polya type. Another consideration was the occasional disparity in size between the gastric and jejunal stoma. When the diameter of the gastric



Figure 3.—(Left) Demonstration of small gastric mucosal prolapse just distal to the stoma. (Right) Reduction of prolapse, with mass in the gastric pouch.

remnant is greater than that of the jejunotomy, the piled-up gastric mucosa is pleated about the stoma, tending to prolapse subsequently.

Grimoud and coworkers⁴ theorized that hypermobility of the mucosa secondary to edema of the submucosal layer and hypertrophy of the mucosal folds are necessary to generate mucosal prolapse. These changes, combined with the technical considerations posed by LeVine, may explain the pathogenesis of the gastrojejunal mucosal prolapse.

Our observations in Case 1 provide convincing evidence that, whatever the initiating factors, the process may be a progressive one. Edema is known to be a factor in the size of the mass. The proliferation of gastric mucosa, however, is as-

sumed to be the factor that transforms a frequently asymptomatic postoperative remnant into disabling illness.

The critical elements of mucosal prolapse are the possibilities of either obstruction or hemorrhage. In the absence of these complications and with negative gastric cytologic results, periodic follow-up examinations would seem appropriate.

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Lactic Acidosis with Recovery In Diabetes Mellitus On Phenformin Therapy

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WALKER AND LINTON¹ were the first to report severe metabolic acidosis associated with only mild hyperglycemia in diabetic patients receiving phenformin. One of the two patients whose cases they reported died, and on pathologic examination no lesion was found to account for his death. Since then, several reports of fatal metabolic acidosis in diabetic patients taking phenformin have appeared in the literature.²⁻⁹ In all these cases lactic acidosis was incriminated as the cause of the metabolic acidosis. Lactic acidosis has been defined as a metabolic acidosis characterized by significant reduction in arterial pH and the presence of significant accumulation of lactate in the extracellular fluids.

The role played by phenformin in these cases is uncertain, for lactic acidosis has occurred in diabetic patients in the absence of phenformin therapy, as reported by Daughaday and coworkers¹⁰ and by Waters et al.¹¹ In almost all the cases reported renal insufficiency was a common feature, and some degree of anoxia was thought to be the precipitating factor.

Herein reported is a case of lactic acidosis in a patient with normal renal function. There was no evidence of associated precipitating factors, such as hypoxia, shock or bleeding, before or during the period the patient was treated. The dose of phenformin, however, had been increased a

few days before the appearance of coma. There are two previous reports of cases in which lactic acidosis occurred after the ingestion of an extra dose of phenformin.^{8,12}

Report of a Case

A 59-year-old Chinese woman who spoke no English was admitted for the first time to The Hospital of the Good Samaritan Medical Center, 7 July 1966, for elective surgical removal of a cataract of the right eye. The patient was known to have had diabetes mellitus for four years, and it had been controlled with diet and phenformin (DBI® capsules 50 mg twice daily). On admission she was alert and in no acute distress, appearing healthy. The blood pressure varied between 130/80 and 106/70 mm of mercury, the pulse was regular at a rate of 90, and respirations were 20 per minute. The patient was 4 feet 11 inches tall and she weighed 118 pounds.

Ophthalmoscopic examination showed bilateral cataracts. The remainder of the physical examination was unremarkable.

On urinalysis there was a specific gravity of 1.017, pH 5.5, a trace of protein, and no glucose or acetone. The hematocrit was 44 percent, and the hemoglobin was 14.9 grams per 100 ml. Leukocytes numbered 8,500 per cu mm with a normal differential count. The fasting blood glucose was 163 mg per 100 ml, and the blood urea nitrogen 29 mg per 100 ml.

The patient received phenformin, 50 mg daily the first three hospital days, then 100 mg the day of operation (fourth day) and thereafter. The cataract was removed under local anesthesia and recovery was uneventful until, four days after operation, the patient complained of nausea and vomited undigested food. The following day she had poor appetite and vomited once. She was unhappy in the hospital, in part owing to difficulty in communicating with the attendants, did not like the food, and was eager to go home. Two days later she felt weak, passed liquid stools on three occasions, and refused to eat. She was discharged nine days after operation at her own and her family's insistence because her emotional state was considered the cause of the anorexia and gastrointestinal symptoms. The fasting blood sugar the day of discharge was 112 mg per 100 ml. During the last five days in hospital the urine had shown two plus acetone and remained negative for sugar. The last four days in hospital the patient had

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TABLE 1.—Summary of Laboratory Data and Fluid Intake and Output in a Diabetic Patient on Phenformin Therapy Who Developed Lactic Acidosis

Hours From Beginning of Treatment	Serum Levels							Parenteral Therapy							Urine	
	Na+	K+	Cl—	CO ₂ —	Glucose	BUN	Lactate	Fluid	Na+	K+	Cl—	HOCs—	Glucose	Insulin	pH	ml.
	(mEq/l.)	(mEq/l.)	(mEq/l.)	(mEq/l.)	(mg./100 ml.)	(mg./100 ml.)	(mM/l.)	(ml.)	(mEq/l.)	(mEq/l.)	(mEq/l.)	(mEq/l.)	(Grams)	(IV) (SC)		
0	140	6.9	103	4.5	195	93	15.0	—	—	—	—	—	—	—	4.5	
3	157	4.7	100	9	630	87		1500	495	—	138	357	70	20	25	8
5	164	3.5	—	13	330	57		—	150	40	40	150	—	25	—	
7	171	3.0	108	18	195	54		1375	195	13	13	195	75	—	15	2185
14	171	3.6	105	25	85	54			89	40	40	89	100	30	25	
18	167	4.1	113	32	65	70	9.8		—	40	40	—	35	15	—	7.5
32	165	4.4	—	36	155	43		3150	—	53	53	—	140	25	—	1940
TOTAL:								6025	929	186	324	791	420	115	65	4125

received three 50 mg capsules of DBI daily for a total daily dose of 150 mg against 100 mg a day previously. She was discharged 18 July but readmitted in coma the next day with Kussmaul respirations at a rate of 40 per minute. The blood pressure was 110/60 mm of mercury, pulse 80 and regular, and rectal temperature 37°C (98.6°F). There was no clinical appearance of shock. The skin was cold, and there was no cyanosis. Deep tendon reflexes were absent, and the plantar response was flexor. No abnormality was noted on examination of the chest. The urine gave a negative reaction for glucose and a four plus reaction for acetone. Specific gravity was 1.011 and pH 4.5. The blood glucose was 195 mg and the blood urea nitrogen 93 mg per 100 ml. Serum sodium was 140 mEq, serum chloride 103 mEq and serum potassium 5.9 mEq per liter. The carbon dioxide content was less than 4.5 mEq per liter, the blood ketone and the lactic acid levels were both well above normal range at 30 mg and 137 mg per 100 ml respectively. The hematocrit was 45 percent, hemoglobin 14.4 grams per 100 ml and leukocytes 19,700 per cu mm with normal cell differential. Intensive treatment was begun with intravenous fluids, oxygen, sodium bicarbonate and insulin (Table 1). After three hours of treatment the patient was still unresponsive. Respirations were 28 per minute. Urinary output was good. The blood urea nitrogen was 87 mg per 100 ml and the carbon dioxide content was 9 mEq per liter. The urine gave a four plus reaction for glucose and for acetone. Serum acetone had dropped from 30 to 15 mg per 100 ml.

Five hours after initiation of therapy the patient was still in coma, the blood urea nitrogen was 57 mg per 100 ml, and the carbon dioxide content was 13 mEq per liter. Serum phosphorus, de-

termined only once, was 2.0 mg per 100 ml. Vital signs were stable. An incomplete electrocardiogram showed a sinus rhythm at a rate of 80 per minute with an occasional nodal ectopic beat and a prolonged QT interval with large, wide T-waves compatible with hypopotassemia. Because of the presence of moist rales at the base of the right lung, the patient was digitalized, but the drug was subsequently discontinued. A film of the chest made with a portable x-ray machine showed no gross increase in the cardiac size compared with a film taken ten days before. No definite parenchymal infiltrations were noted.

Fourteen hours after admission the patient started to respond. The skin was warm and dry. The blood urea nitrogen was 54 mg per 100 ml, and the carbon dioxide content was 25 mEq per liter. The urine was still four plus for acetone, serum lactate was 88 mg per 100 ml (9.8 mM per liter) and there was no ketone content. Twenty-four hours later the patient was alert and responded to questions. The urine was negative for sugar and acetone. The blood urea nitrogen was 16 mg and lactate 38 mg per 100 ml (4.2 mM per liter) and carbon dioxide 28 mEq per liter. The patient was able to take fluids by mouth. A complete electrocardiogram at this time showed a normal QT interval, but with diffuse T-wave inversion evident in standard Leads II and III, aVF, and precordial leads v₂ through v₆. A tracing taken the following day, 21 July, showed essentially the same T-wave changes with again some prolongation of the QT interval. No further electrocardiograms were obtained.

The patient was discharged ten days later with prescription of a 1,800 calorie diabetic diet and chlorpropamide (Diabenese®) 250 mg daily. On the day of discharge the blood urea nitrogen was 21 mg per 100 ml and the two-hour postprandial

TABLE 2.—Summary of Reported Cases of Lactic Acidosis in Diabetic Subjects on Phenformin Therapy

Author and Reference Number	Age Years	Sex	Renal Status Before Acidosis	Associated Conditions at Time of Acidosis	Blood Chemistries Reported at Time of Recognition of Acidosis				Outcome
					CO ₂ — mEq/l	lactic acid mM/l*	pyruvic acid mM/l*	BUN mg/100 ml	
Tranquada et al. ³	69	F	BUN 29	Shock	5.0	25.0	0.86	82	Died
	74	F	BUN 47	Infection	8.0	30.8	0.72	42	Died
	68	F	BUN 70	Myocardial infarction	5.0	27.7	0.89	120	Died
Bernier et al. ⁴	69	F	Chronic renal disease, moderate	Shock	2.0	20.9	0.49	—	Died
	40	F	Chronic renal disease, moderate	Hypotension. Infarct, small bowel.	5.0	18.0	0.45	21	Died
Mengis ⁶	68	M	Normal kidneys at autopsy	Shock 5th day post TUR	3.0	—	—	—	Died
	66	M	Mild arterioneuro-sclerosis, autopsy	Hypotension Cyanosis	3.6	31.0	1.7	42	Died
Ball et al. ⁷	61	F	Mild arterioneuro-sclerosis, autopsy	Hypotension	5.0	12.0	0.8	53	Died
Proctor and Stowers ⁸	64	F	Normal	Hypotension Hypothermia	5.8	26.7	—	140	Died
Young and Amanino ⁹	69	F	BUN 125 (urinary tract infection)	—	4.4	23.0	1.0	44	Died
	62	F	BUN 18	Hypotension	8.7	12.0	—	108	Survived
Gottlieb et al. ²	49	F	Normal	Hypothermia	4.6	—	—	34	Survived
				Hypotension					
Ewy et al. ⁵	45	F	BUN 70 proteinuria	Hypotension	<4.0	10.0	0.5	70	Survived
Lacher and Lasagna ²⁰	43	M	Not mentioned	Angina pectoris Normotension	9.0	10.0	—	21	Survived
Johnson and Waterhouse ¹²	44	F	Proteinuria	Gangrene Obesity	6.0	9.5	0.19	57	Survived
	70	F	Azotemia. Chronic pyelonephritis	Hypoglycemia	5.0	14.4	0.25	77	Survived
Present Case	59	F	BUN 29	Normotension	<4.5	15.0	—	93	Survived

*Normal Values: Lactic Acid 0.6-2.2 mM/l. (5-20 mg./100 ml.)
Pyruvic Acid 0.06-0.2 mM/l. (0.5-1.7 mg./100 ml.)

blood sugar was 250 mg per 100 ml. The blood pressure was 130/70 mm of mercury. The urine gave a one plus reaction for glucose and was negative for acetone. The patient weighed 105 pounds on the day of discharge.

Seen as an out-patient a week following discharge the patient was doing well except for complaint of weakness and sleepiness. Vital signs were all normal. She appeared entirely normal and the findings on physical examination were within normal limits. The three-hour post-prandial blood sugar at this time was 205 mg per 100 ml. The urine was negative for sugar and acetone. When the patient was seen a month later and two months later blood sugar was 153 mg and 162 mg per 100 ml respectively. Body weight had increased to 119½ pounds, blood pressure was 160/80 mm, and on physical examination she appeared in good health except for ventricular ectopic beats. On telephone follow-up a year later she was reported to be well, and her weight 120 pounds.

Discussion

Ungar and coworkers¹³ observed that phenformin brought about hypoglycemia in eviscerated or alloxan diabetic animals. Clinical use of the drug in diabetic patients was reported by several investigators.¹⁴⁻¹⁶

Hyperlactatemia and hyperpyruvatemia have been a consistent finding during phenformin therapy.¹⁷ Hall and coworkers¹⁴ described acetonuria with normoglycemia in 11 of 35 diabetic patients on phenformin therapy. Walker and Linton¹ and Walker and Hannah¹⁸ noted ketonuria in one-third of their patients treated with phenformin, with frank reduction of alkali reserve in 13 of a total of 117. These investigators postulated an increase in blood lactate levels as the cause of acidosis, but no blood determinations were made at that time. Tranquada and coworkers³ reported three cases in which patients with diabetes who were receiving phenformin therapy died in metabolic acidosis. In all three cases blood lactate levels were very high and there was a dispropor-

tion in the lactate:pyruvate ratio. In these patients there were other causes which are known to produce lactic acidosis in addition to the administration of phenformin. Shock was the predominant feature in two of them. The question of whether phenformin provokes lactic acidosis in diabetic patients is as yet unsettled,¹⁹ although the present case suggests that it may alone be the cause.

In a review of the literature, 16 cases were found of metabolic acidosis in diabetic patients on phenformin therapy (Table 2). Despite intensive therapy ten of the patients died of acidosis. Common features present in these patients were sudden onset of acidosis, and in six patients preexisting renal failure. The case reported by Proctor and Stowers⁸ is somewhat similar to the one here presented, in that lactic acidosis developed after ingestion of 50 mg of the drug in excess of the patient's normal dose, a total of 150 mg in 12 hours. The patient in that case died. In six of the 16 reported cases the patient survived and in one the blood urea nitrogen was normal during the period of acidosis.²⁰ In the case reported by Gottlieb et al² the blood urea nitrogen returned to normal after two weeks. In one of the cases reported by Young and Amanino⁹ the blood urea nitrogen was normal before the episode of acidosis. In one reported case hemodialysis was carried out and the patient recovered. In addition to the 16 cases reported, another five^{1,18,21-23} had been mentioned in the literature without a formal report; three of the five patients died.

According to Tranquada,^{23,24} serum lactate levels lower than 7 to 8 mM per liter cannot be considered indicative of lactic acidosis. The blood levels in patients taking phenformin is in the range of 2 to 3 mM.⁴

In the present case no clear reason for her coma, beyond the administration of phenformin, was evident. One of the factors that could have precipitated coma was that she had not eaten well for three days. This, plus nausea, diarrhea and vomiting, could have accounted for the presence of acetone in the urine. The gastrointestinal symptoms may well have been the result of increased phenformin dosage, however. The decreased fluid and food intake may have produced dehydration, leading to development of azotemia of extrarenal origin. It has been suggested that the major route of disposal of phenformin and its metabolites is through the kidneys.²⁵ This accumulation of the drug in the blood could precipitate lactic acidosis

in a patient without signs of hypoxia. The dose of phenformin had increased approximately five days before coma appeared. In another reported case in which the dose of phenformin had been increased, lactic acidosis developed approximately 12 hours after the onset of symptoms, and the patient died despite intensive therapy.⁸ In one of the two cases reported by Johnson and Waterhouse¹² the administration of phenformin had been started the day before admission to hospital, and in the other the dose had been increased nine days before coma developed.

In the present case treatment was very aggressive and directed mainly to correction of the acidosis. Fortunately, the urinary output was excellent and there were no concomitant pathologic conditions such as hypoxia, hypotension, shock or myocardial infarction, to cause complications. Another important factor in the favorable outcome may have been the rather moderate elevation of lactic acid in the blood at the time therapy was started. In fatal cases the blood lactate levels were higher and there were associated serious illnesses. Johnson and Waterhouse¹² were of the opinion that intravenous glucose and insulin produced definite improvement in patients who had been refractory to the administration of sodium bicarbonate.

Summary

A case of lactic acidosis is reported in a 59-year-old Chinese woman who made complete recovery. The case is unusual in that it appeared that the lactic acidosis followed an increase in dose of phenformin from 100 to 150 mg a day. There was an associated decrease in food and fluid intake from nausea and vomiting, and rapidly developing coma with serum lactic acid of 137 mg per ml (15 mM per liter).

Aggressive therapy with sodium bicarbonate, oxygen, parenteral fluids, and insulin was carried out. The patient was well at the time of last report a year later.

TRADE AND GENERIC NAMES OF DRUGS

DBI®phenformin hydrochloride
Diabinese®chlorpropamide

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BRONCHIAL IRRITATION FROM FREON NEBULIZERS

"An important cause of bronchial irritation is the use of the Freon nebulizer. Many patients with chronic lung disease will have a medihaler in one pocket and a mistometer or bronchometer in the other. They're the two-gun patients. They treat the back of their throat at every moment; every 20 minutes, every 10 or five minutes, they spray the back of their throat with this material which has a pH of about two or three. It's highly acidic. I think one or two of them are buffered, but they are quite irritating when they are used in this manner. And of course, the recurrent vasoconstriction of an ill patient is also damaging. That is not the way they were designed to be used, and they have become a very important factor in causing increased bronchial irritation. A lot of the so-called 'paradoxical bronchospasm' from bronchodilators is due to the use of bronchodilators incorrectly, due to the use of isoproterenol or any of the commercial bronchodilators undiluted in a machine, or due to the use of the sprayers too frequently; if one needs an aerosol bronchodilator, he should make sure that it's well diluted (by which I mean 5 or 6 cc of boiled or distilled water plus 0.25-0.5 cc of 1:200 isoproterenol or some similar medication . . .) and use this medication every three or four hours—thoroughly when used—and not in between. The Freon nebulizer should not be used by patients with pronounced inspiratory obstruction because rapid inspiration is necessary to get the medication adequately distributed."

—BEN V. BRANSCOMB, M.D., Birmingham
 Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 2, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Progress in Disseminated Intravascular Coagulation

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THE PAST FEW YEARS have brought many new developments in the field of disseminated intravascular coagulation. To the practitioner of medicine, many of these may seem to represent advances that are of interest but not of importance since they appear to be related more to experimental or research medicine than to clinical medicine. However, with the concomitant advances in therapy, the possibility of prevention of morbidity and mortality in certain human diseases becomes more likely. In fact, the major recent effort in disseminated intravascular coagulation has been the attempt to control the clotting in these diseases at a clinical level. The results have been variable. During this period of rapid change, it seems worthwhile to take a circumspect look at the field, with the object in mind of examining the lessons learned from some of these clinical trials and attempting to evaluate what the experimental observations may imply for the future of clinical medicine. Another object of this review is to bring together those diseases in which disseminated intravascular clotting has recently been demonstrated to play a role.

In order to put the problem in its proper context, certain general principles must be understood.

Nature of the Problem

An Intermediary Mechanism of Disease

Disseminated intravascular coagulation is an intermediary mechanism of disease.¹ Behind every

clotting episode lies an etiologic factor that triggers the clotting. The major categories of etiologic factors causing intravascular coagulation are: (1) intravascular hemolysis, (2) release of tissue thromboplastin, (3) bacterial endotoxin, (4) proteolytic enzymes, (5) particulate or colloidal matter, (6) anoxia and anoxemia, (7) endothelial damage and (8) ingestion of certain lipid substances.

Each disease process has its own unique clinical and pathologic changes in addition to those associated with intravascular clotting. It is obvious that the best prevention and treatment of intravascular coagulation lies in the prevention and treatment of the underlying disease.

Definition

Disseminated intravascular coagulation encompasses more than the simple formation of a thrombus. It is a biologic process involving many chemical substances and physiologic responses. It begins with the entry of a procoagulant material or activity into the circulating blood; it progresses to the stage of platelet aggregation and fibrin formation which may or may not result in thrombosis of capillaries, arterioles and venules of various organs; it is associated with activation of the fibrinolytic enzyme system with dissolution of fibrin and fibrinogen and the release of fibrin-split products into the plasma; and it is not complete until the hemostatic mechanism and vasomotor apparatus have returned to normal and the last significant amount of fibrin-split product has been cleared from the blood.

In some patients activation of the fibrinolytic system is minimal and intravascular clotting is the major problem, whereas in other patients the fi-

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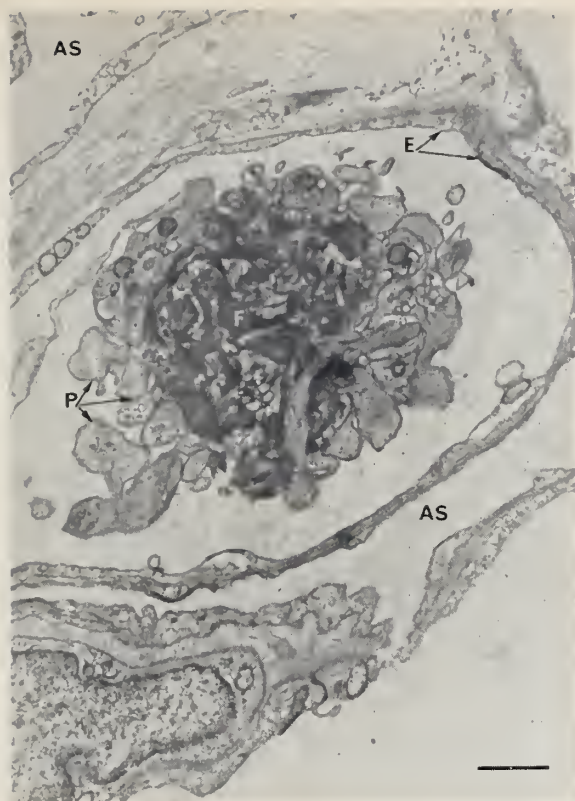


Figure 1.—Endotoxin shock. A pulmonary capillary contains a mass of fibrin and platelets, some of which are undergoing viscous metamorphosis. Electron micrograph. $\times 16,000$. AS=Alveolar space. E=Capillary endothelium. P=Platelets. F=Fibrin.

brinolytic system is rapidly and massively activated so that fibrinolysis overshadows the initiating clotting process.

It should be emphasized that disseminated intravascular coagulation may be quite extensive or severe without the development of occlusive thrombi. Considerable clotting may occur and not be visible by light microscopy. In some instances this is due to lysis of thrombi. In others it is because the fibrin is submicroscopic and can be detected only in electron microscopy. An example is endotoxin shock in monkeys, in which no thrombi appear in the light microscope but fibrin strands are visible by electron microscopy.²

Diagnosis

Evidence of disseminated intravascular coagulation comes from four sources: (1) pathologic examination, (2) examination of the hemostatic mechanism, (3) the clinical manifestations and (4) the response of the hemostatic mechanism to a therapeutic trial of heparin.

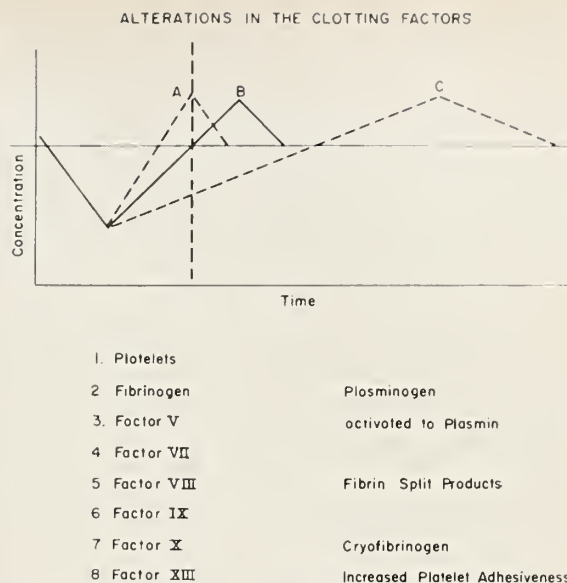


Chart 1.—Schematic representation of the effect of a single large intravascular clotting episode on the hemostatic mechanism. The top horizontal line represents 100 percent concentration or levels of all Factors. All Factors fall proportionately immediately. Following this they recover and rise to above normal values. The rate of return and overshoot is dependent on the rate of regeneration of each individual Factor. Line A represents Factor VIII; Line B = Fibrinogen; Line C = Platelets.

The hypothetical vertical line (dash) shows that a single determination of these Factors at this time may yield a high level of Factor VIII, a normal level of fibrinogen and a low platelet count.

Pathologic Evidence

In the majority of these diseases, tissue examination reveals platelet or fibrin thrombi, or both, in the arterioles, capillaries or venules of many viscera. If these microscopic thrombi are of sufficient duration they are associated with hemorrhage or ischemic necrosis of the organ involved. The organs most frequently involved are the kidney, brain, pituitary, lungs, liver, adrenal glands and mucosa of the gastrointestinal tract (Figure 1).

The severity of involvement of an organ is variable from one disease to another and from one patient to another with the same disease. The spectrum of damage is exemplified by the kidney, in which there may be evidence of (1) no disease, (2) "lower nephron nephrosis" or acute focal tubular necrosis, or (3) bilateral renal cortical necrosis. The brain may exhibit (1) no changes, (2) capillary platelet thrombi, (3) capillary fibrin thrombi, (4) perivascular ring hemorrhages, or (5) focal infarcts. The pituitary may show (1) no change, (2) capillary fibrin thrombi, (3) focal hemorrhage, or (4) extensive infarct necrosis. In

patients who survive the acute process the necrotic lesion evolves into a collagenous scar. The liver may reveal (1) no anatomic change, (2) sinusoidal platelet or fibrin thrombi, (3) hemorrhage, (4) focal necrosis of liver cells, or (5) extensive infarction. The adrenals may exhibit (1) no anatomic alteration, (2) platelet and fibrin thrombi in the sinusoids, (3) focal hemorrhage or necrosis, or (4) diffuse hemorrhagic necrosis. Involvement of the gastrointestinal tract is extremely variable. The mucosa is predominantly involved and this may include the mucosa from the esophagus to the colon. Gross observations include no change, petechiae, ecchymoses, small focal ulcers, large multiple ulcers to pseudomembranous enterocolitis. The lung may show no change, platelet and fibrin thrombi, or focal alveolar hemorrhage.

The presence of microscopic thrombi in multiple organs constitutes proof of the reaction although it does not indicate the duration or severity of the clotting episode.

The Hemostatic Mechanism

Intravascular coagulation produces a characteristic sequence of changes in components of the hemostatic mechanism. Initially, there is a decrease in platelets, circulating fibrinogen, prothrombin complex, Factors v, vii, viii, and x (Chart 1). This depletion is due to the fact that these substances are used up in the process of coagulation and to the activation of plasminogen with the formation of active fibrinolysin which further diminishes the concentration of fibrinogen and certain other factors by enzymatic degradation. Intravascular clotting and fibrinolysin activation usually occur simultaneously. Although, in disease states, activation of the fibrinolytic system is almost always preceded by intravascular coagulation, there are some diseases in which intravascular coagulation predominates and fibrinolysin activation is minimal or slow. In other conditions fibrinolysin activation is rapid and maximal and may overshadow the initial activation of the clotting mechanism.

The initial period of depletion of clotting factors is followed by a recovery period, and this is characterized by elevation of these components above normal. During this rebound the abnormally high levels of any one factor may vary from 100 percent to 200 percent of the normal concentration. Subsequently, with the recovery of the patient, the values return to normal. The time at which the

peak of overproduction of any one factor is reached is dependent upon its half-life and rate of synthesis. The half-life of platelets is much longer than that of Factor viii, and the peak of overproduction of platelets is a matter of days while that of Factor viii is a matter of hours. The duration of the stimulus to clotting and fibrinolysin activation also determines the rate of recovery, the latter being considerably slower when the stimulus acts over a long period of time and more rapid when it is of short duration.

Other changes in the hemostatic mechanism include the appearance of increased platelet adhesiveness, increased amounts of cryofibrinogen and antithrombin, and initial depletion of fibrin stabilizing factor (Factor xiii).

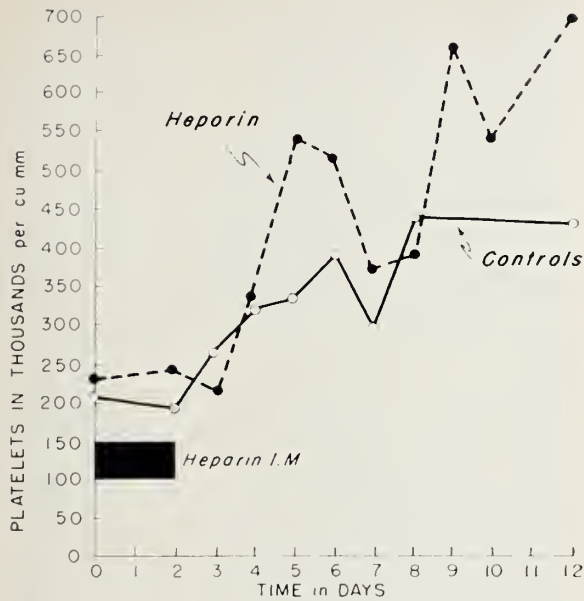
Clinical Manifestations

In spite of the varied clinical picture in these diseases, which one would expect from the variety of etiologic agents, certain clinical events occur with great frequency in patients with severe acute disseminated intravascular coagulation.³ These are hypotension (shock), a bleeding tendency, oliguria or anuria, convulsions and coma, nausea and vomiting, diarrhea, abdominal pain, back pain, dyspnea, and cyanosis. Such a constellation of clinical signs and symptoms regardless of the etiologic agent or the presence of other signs and symptoms, particularly when they occur almost simultaneously, is presumptive evidence of disseminated intravascular coagulation.

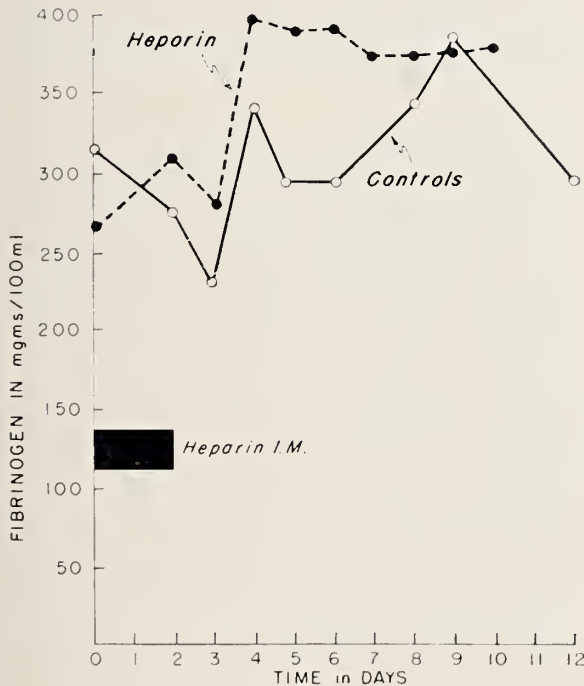
The hypotension may be mild or severe, transient or irreversible. The hemorrhagic diathesis may consist only of the appearance of a few petechiae on the skin or mucous membranes, or it may show any degree of severity up to the development of totally incoagulable blood with massive internal or external hemorrhages. The same variability may be observed in renal function. There may be transient oliguria, anuria for several days followed by diuresis, or irreversible anuria and death in uremia.

The variations in tissue reaction, hemostatic mechanisms, and clinical manifestations are due to variations in the rate, amount and localization of intravascular coagulation. These can be ascribed to the following: (1) differences in the potency of the clot-promoting agent; (2) differences in quantity of the agent; (3) difference in portal of entry of the agent; (4) differences in the condition of the vascular bed at the time clotting takes place;

PHILIPPINE HEMORRHAGIC FEVER Platelets



PHILIPPINE HEMORRHAGIC FEVERS Fibrinogen



Charts 2 and 3.—Response of platelets and fibrinogen to heparin trial in Philippine Hemorrhagic Fever. (Twenty patients in each group.)

and (5) rate and extent of activation of the fibrinolytic system.

It is also important to note that multiple mechanisms may operate to trigger clotting in any one disease. The process may become a vicious cycle particularly with the development of shock which, in itself, can be responsible for causing a certain amount of intravascular coagulation.

Response to a Therapeutic Trial of Heparin

The response to heparin may be clinically apparent in those diseases in which patients exhibit a hemorrhagic diathesis. Not infrequently, heparinization stops the oozing from the gums, the gastrointestinal tract or the uterus.

The administration of heparin to patients with disseminated intravascular coagulation usually results in a return toward normal levels of all the factors of the coagulation mechanism. As in the cases with a spontaneous recovery, the different factors return at different rates. For the most part the response is rather slow, with fibrinogen and platelets returning to almost normal values within three to five days (Charts 2 and 3). Of course, the beginning of the trend back may be observable within the first 24 hours. This response to heparin indicates two things: (1) that intravascular coagulation is occurring in the patient and (2) that the intravascular clotting is associated with the release of thrombin or thromboplastin into the circulation (since heparin is both antithrombic and antithromboplastic).

A word of caution concerning the interpretation of such data is necessary. The spontaneous recovery of a patient is accompanied by a spontaneous recovery of the hemostatic mechanism after a single massive episode of disseminated intravascular coagulation. Thus, to ascertain the effectiveness of heparin the rate of recovery of the hemostatic mechanism after its use in any single patient must be compared with either the rate of recovery in other similar patients without heparin, or with the trial of other therapeutic agents in the same patient which have failed.

With these few general principles in mind, we shall turn to those diseases in which the occurrence of disseminated intravascular coagulation has recently been discovered. Although disseminated intravascular coagulation is ubiquitous and knows no categorical limitations, it may be useful

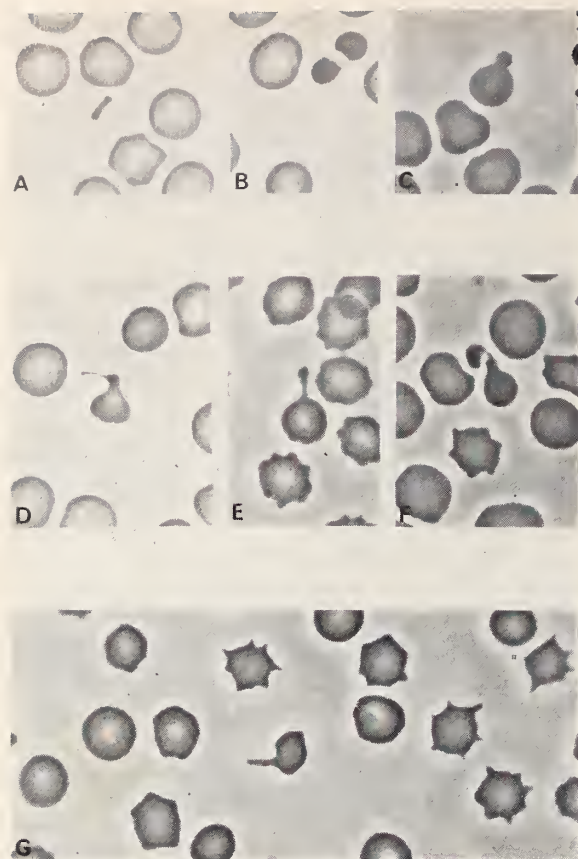


Figure 2.—Films of peripheral blood. Phase contrast microscope. Wright's stain. A, Elongated red cell fragment. B, Red cell cut in half with dense cytoplasm. C, Red cell with "bud" from surface and dense cytoplasm. D, E, F, and G, Various types of elongated "tails" on red blood cells. These present a similar appearance to the distorted cells in the lung and spleen observed by electron microscopy. The "crenated" cells were more numerous in the terminal phases of the experiments.

to consider them with respect to the medical specialty to which they are related.

Internal Medicine

Microangiopathic Hemolytic Anemia

The term *microangiopathic hemolytic anemia* was introduced by Brain, Dacie and Hourihane⁴ as a label for hemolysis of a type found in association with thrombotic thrombocytopenic purpura, the "hemolytic-uremic" syndrome, polyarteritis nodosa, some cases of malignant hypertension and in certain patients with carcinomatosis. Disseminated intravascular coagulation occurs in all these diseases.¹

The simplest and most rapid means of recognizing hemolysis of this type lies in the examination of the blood film. Characteristically, the red

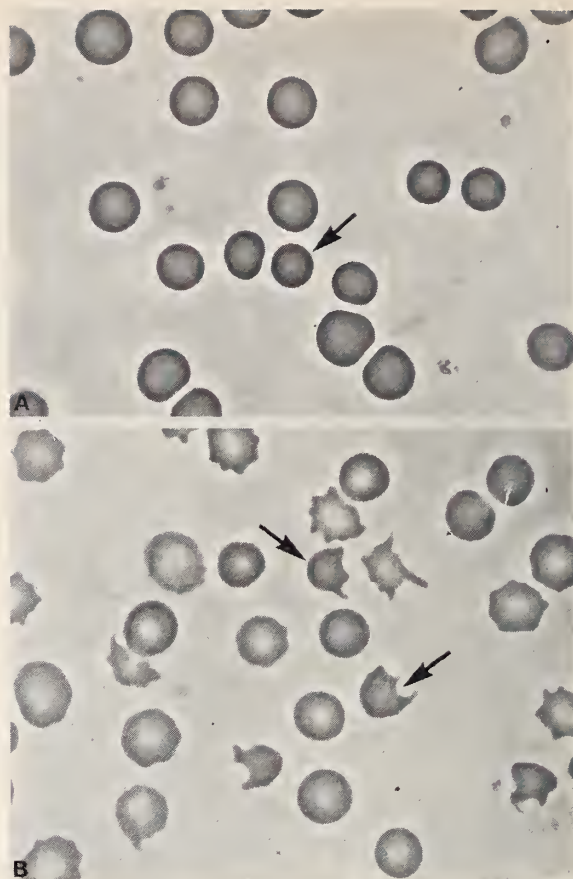


Figure 3.—Films of peripheral blood. Phase contrast microscope. Wright's stain. A, The small densely stained cells (arrows) are microspherocytes. B, The arrows indicate ("helmet cells") typical of microangiopathic hemolytic anemia.

blood cells are altered to a variety of bizarre but readily recognized shapes.⁵ Among these are "helmet cells," "burr cells," crenated cells, schistocytes (cell fragments) and microspherocytes (Figures 2 and 3). These structural alterations are also accompanied by an increased osmotic and mechanical fragility. They may be accompanied by rises in the reticulocyte count, plasma hemoglobin, increased indirect plasma bilirubin and hemosiderinuria, depending on the severity and rate of the hemolysis.

In the past, these alterations in the red cell have been attributed to azotemia which frequently, but by no means always, accompanies these diseases. However, there is now ample clinical and experimental evidence to show that they are caused by disseminated intravascular coagulation. This was first suggested by Brain and coworkers (1962) who noted that the most pronounced structural alterations of the red cells occurred in patients

with necrosis and fibrin deposition in arterioles and capillaries. Further evidence came from their experimental studies with bacterial endotoxin.^{6,7} Using doses of endotoxin which elicit the generalized Shwartzman reaction, they observed changes in the red cells characteristic of "microangiopathic hemolysis." They also infused thrombin into the circulation and produced the same effect. This is as direct a means of producing disseminated intravascular coagulation as is now available. Curiously, with thrombin, the effect was minimal, but when epsilon aminocaproic acid (EACA) was added to prevent lysis of thrombi, the hemolytic effect was greatly enhanced. An extract (arvin) derived from the venom of Malaysian pit viper which induces intravascular clotting had the same effect on the red cell.

The formation of hemoglobin-containing fragments suggested that the membrane of red cells had sustained localized damage and then had resealed. Such damage must have been mediated by an agent with physical dimensions that were small relative to the size of a red cell — and fine fibrin strands possess the necessary physical characteristics.

To test this idea under direct observation *in vitro*, a simple circuit was constructed around which blood could be pumped while a fibrin thrombus was in the process of formation.⁸ Coagulation was initiated by introducing small amounts of thrombin or snake venom into the circuit. By controlling the rate of build-up of thrombus, the pressure to which the blood was exposed was maintained within physiological limits. The passage of blood through these fibrin clots resulted in hemoglobinemia and red cell fragmentation (Bull 1968). Microscopic examination of this process revealed many individual red cells attached to or folded over single fibrin strands. Red cells in various stages of hemolysis could be seen in the heavy fibrin columns. The investigators concluded that fragmentation occurs when a rapidly moving red cell encounters a thin fibrin strand. The red cell becomes attached to or folded about the strand. Such a cell is subjected to buffeting from unattached red cells and hence to forces which may tear the membrane. If the tear takes place along the line of the fold at the site of membrane apposition, two hemoglobin-containing fragments may form with loss of little, if any, hemoglobin. Tears at other sites of the membrane will result

in partial loss of hemoglobin and the formation of irregularly shaped fragments.

One need not consider that *in vivo* the fibrin strands are stationary as in the *in vitro* experiments of Bull and Brain (1968). It is worth emphasizing that one of the characteristic features of disseminated intravascular coagulation is that the fibrin is forming in a moving stream of blood. As a modification of Brain's concept, it may well be that the fibrin forms in larger vessels and traps red cells within it, and the trauma which fragments the cells comes when the moving mass suddenly impinges against smaller vessels such as arterioles, capillaries, or (on the venous side) against the small vessels of the pulmonary circulation. The red cells would be squeezed out of such a loose fibrin mesh at the time of impact.

Brain⁹ recently described his experience with the use of heparin in patients with "microangiopathic hemolysis." Four patients were infants with the "hemolytic-uremic" syndrome and three were young women with pre-eclamptic toxemia of pregnancy or shock and a hemorrhagic diathesis. Not only did the clotting mechanism return toward normal, but the hemolysis was stopped as evidenced by a drop in the plasma hemoglobin and a disappearance of the fragmented red blood cells.

We have recently¹⁰ made some observations on the mechanism of hemolysis in experimental catecholamine shock which may be related to certain diseases of man. The continuous infusion of epinephrine in high doses into monkeys and rabbits caused shock, disseminated intravascular coagulation and hemolysis. The hemolysis was characterized by an elevation of plasma hemoglobin, an increase in osmotic fragility, and changes in the shapes of red blood cells. The structural alterations in the red cells in the circulating blood included "helmet" cells, crenation, schistocytes and microspherocytosis. The spherocytosis was correlated with an increased osmotic fragility. *In vitro* studies demonstrated that the hemolysis was not due to release of hemolytic substance into the plasma, nor to a direct action of epinephrine on the red cell.

Blockade of the alpha-adrenergic receptor sites by Dibenzylamine[®]* (phenoxybenzamine hydrochloride) completely prevented the hemolysis, as well as the intravascular coagulation. It was concluded that the hemolysis was mediated by the stimulation

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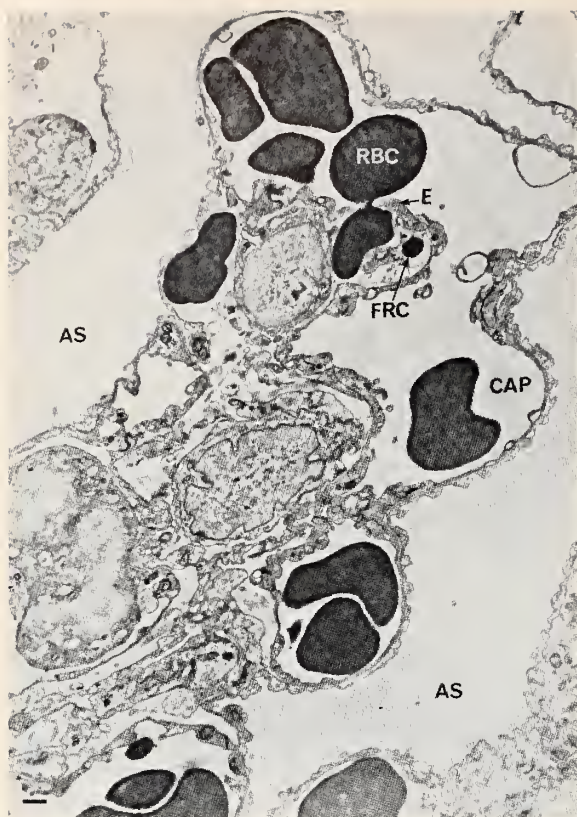


Figure 4.—Rabbit lung. A red blood cell is seen traversing a small gap in the endothelium. The mechanical stress producing such a distorted cell may be responsible for some of the red cell fragmentation caused by epinephrine infusion. $\times 5,300$. RBC=Red blood cell. E=Endothelium. FRC=Fragmented red cell. CAP=Capillary lumen. AS=Alveolar space.

of the alpha-adrenergic receptor sites in small vessels.

In general, the severity of hemolysis correlated with the amount of intravascular clotting. Pretreatment of the animals with heparin greatly reduced the amount of hemolysis, but did not completely prevent it. This suggests that some other mechanism besides intravascular coagulation is in action.

Electron microscopy of the tissues of these animals revealed another mechanism. Red blood cells were found traversing small gaps in the endothelium of the capillaries of the lung and sinusoids of the spleen (Figure 4). Passage through the capillary walls produced distortion of the cells with large cytoplasmic extensions and fragmented cell membranes. These changes were of more than a temporary nature since they were found in red cells in the circulating blood both by light and electron microscopy. It seems likely that the mechanical distortion produced by this "pinching" process is in part responsible for cell membrane

damage, spherocytosis and ultimately some hemolysis. The hemolysis produced by epinephrine infusion resembles that which occurs in the "microangiopathic hemolytic anemia" syndrome and is ultimately due to (1) disseminated intravascular coagulation, (2) distortion and fragmentation of red cells in their passage through gaps in the capillary epithelium and (3) the acquired spherocytosis.

From the clinical standpoint, this phenomenon has great interest because it is now possible to detect the occurrence of disseminated intravascular coagulation by the simple expedient of making a blood smear. The observation of the characteristic structural alterations of the red blood cells is strong presumptive evidence of intravascular clotting.

From the standpoint of the etiology and pathogenesis of certain diseases this mechanism of hemolysis is of great interest. For example, in the past we had categorized thrombotic thrombocytopenic purpura as a disease with intravascular coagulation caused by some unknown hemolytic process.¹ However, with the demonstration that disseminated intravascular coagulation can cause hemolysis, the problem of which is cause and which effect must now be explored. The problem can be easily resolved, at least in part, by the simple administration of heparin to these patients with a measurement of the amount of alteration in the rate of hemolysis.

Renal Disease

A recent promising report by Kincaid-Smith¹¹ from Australia serves to focus attention on the role of intravascular clotting in the pathogenesis of certain types of kidney disease. Kincaid-Smith has treated six patients with oliguric renal failure shown histologically to be due to glomerulonephritis or obstructive lesions in arterioles and glomeruli with infusion of heparin, which was given in addition to steroids and immunosuppressive drugs. The rapid improvement in urine output which followed heparin infusion in five of the six patients, and deterioration in renal function when heparin was stopped in three patients, suggested that the heparin had some direct effect on the renal lesion. Steroids or cytotoxic drugs were given before heparin in some patients and after heparin in others, and no obvious improvement was noted at the time of giving these drugs.

To what extent anticoagulation will prove useful

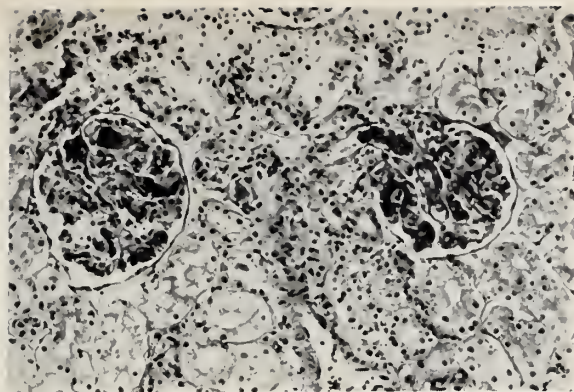


Figure 5.—Glomerular capillary thrombi secondary to acute, massive disseminated intravascular coagulation. Hematoxylin and eosin stain. $\times 160$.

in the management of glomerulonephritis, or other renal diseases, will require testing in many more patients. However, in the meantime it may be worthwhile to consider the various known ways in which fibrin is deposited in the kidney as a background to this clinical consideration.

Thrombosis of the microcirculation. The sudden formation of glomerular capillary thrombi with obstruction to the flow of blood in the renal cortex is perhaps the most extreme form of renal fibrin deposition (Figure 5). This is the basic mechanism of the production of bilateral renal cortical necrosis with total renal insufficiency in man and can be reproduced experimentally by intravenous infusion of thromboplastin,¹² thrombin,¹³ or the appropriate doses of bacterial endotoxin.¹⁴ The studies of Muller-Berghaus^{15,16} indicate that relatively large amounts of fibrin can be deposited in the kidney by this mechanism; amounts equivalent to 56 percent of the circulating fibrinogen. In the experimental animals, the glomerular capillary thrombi induced by bacterial endotoxin can be prevented by intravenous infusion of heparin.¹⁷

Several recent studies dealing with the pathogenesis and prevention of the experimental generalized Schwartzman reaction raise the possibility that agents other than heparin may be useful in preventing this form of ischemic renal damage.

Muller-Berghaus was able to prevent the glomerular-capillary thrombosis caused by bacterial endotoxin in pregnant rats by blockade of the alpha-adrenergic receptor sites by Dibenamine® and Dibenzylamine® (phenoxybenzamine). These experiments indicate that endotoxin-induced glomerular thrombi are localized in the kidney by

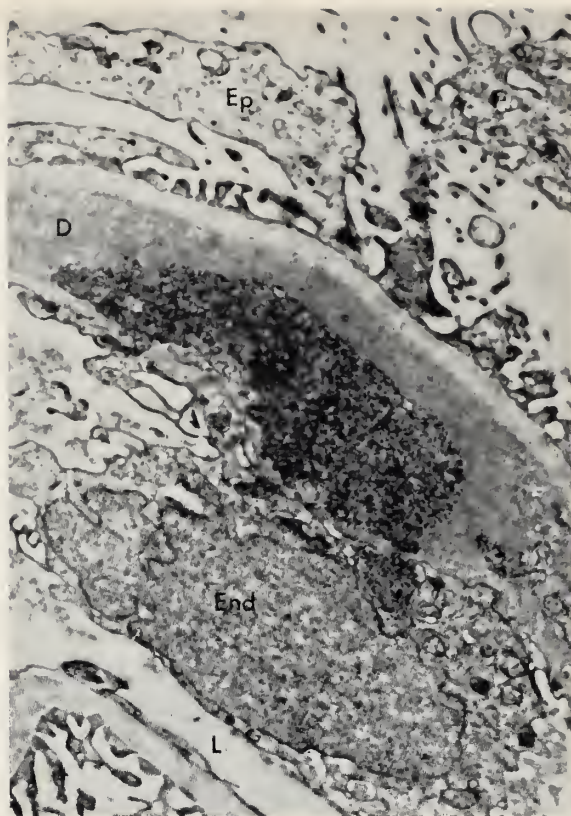


Figure 6.—Toxemia of pregnancy. Renal glomerulus. The basement membrane is normal in thickness. A granular deposit of fibrin is present on the luminal side. The endothelial cell is lifted off the basement membrane and appears to be phagocytizing some of the granular deposit. The epithelial cells are essentially normal. $\times 12,000$. D=Deposit of granular fibrinogen. Ep=Epithelium. End=Endothelial cell nucleus. L=Capillary lumen. (Electron micrograph courtesy of Dr. W. Mautner of the Mt. Sinai Hospital, New York.)

stimulation of the alpha-adrenergic receptor sites. Whether or not alpha-adrenergic blockade for this purpose would be feasible in man remains to be demonstrated.

Evans and Mustard¹⁸ prevented the renal capillary thrombi caused by bacterial endotoxin by use of anti-inflammatory agents including phenylbutazone, sulfinpyrazone and sodium salicylate. They gave these agents intravenously for four hours before the first injection of endotoxin and throughout the experiment. The doses used were: 400 mg per kg per day of sodium salicylate; 200 mg per kg per day of sulfinpyrazone and 150 mg per kg per day of phenylbutazone. In addition to their other actions, all of these agents prevent platelet aggregation *in vitro* and, since platelets are an essential requirement for the evolution of the Schwartzman reaction,¹⁹ the investigators in-

terpreted the results as an effect primarily on the platelets *in vivo*.²⁰ Whether or not lower doses or other routes of administration of these agents would be effective in animals or man remains to be explored.

Renal glomerular filtration. Another mechanism by which fibrin is deposited in the kidney is through the action of glomerular filtration. The human disease which illustrates this best is pre-eclamptic toxemia of pregnancy.²¹ In this disease, there is a stimulus to intravascular coagulation which is mild in nature and chronic in duration. It produces an increased platelet adhesiveness²² and an increased amount of cryofibrinogen in the circulating blood.²³ The fibrin deposits in the glomeruli have quite a different appearance by electron microscopy from the long strands with cross-striations with a periodicity of approximately 200 Angstrom units which occur in occlusive thrombi. The deposits of chronic intravascular coagulation are granular in structure and lie as irregular amorphous masses against the basement membrane on the luminal side (Figure 6). In all likelihood, these deposits represent an incompletely polymerized form of fibrin, possibly a complex of fibrinogen and fibrin monomer which has been accumulated on the basement membrane by the filtering action of the glomerulus. The endothelial cells attempt to phagocytize this material and, in doing so, swell up and lift away from the basement membrane causing a narrowing of the capillary lumen. It is conceivable that these alterations are responsible for the albuminuria and diminished glomerular filtration rate which are characteristic of pre-eclamptic toxemia. This mechanism is also operative in other disease states, most notably in disseminated lupus erythematosus. Also, we have observed this mechanism in animal experiments on Aleutian disease of mink.²⁴ The glomerular fibrin deposits in all these conditions are very much alike and chronic intravascular coagulation has been shown to accompany them. Taking toxemia as the example, these deposits appear to be resolvable since no permanent renal damage occurs following delivery of the patient.

Endothelial cell basement membrane damage. Another mechanism for the deposition of fibrin in the kidney appears when the endothelial cells and basement membrane of capillaries are damaged. This mechanism is found in glomerulonephritis. Although the deposition of fibrin under these conditions may be intravascular, it is also extravascu-

lar and is best thought of as a leakage of plasma from the vessels with clotting of fibrin after exposure to the extravascular environment.

One of the most interesting examples of damage of this type comes from experimental work — that is, nephrotoxic serum nephritis, or “Masugi nephritis.” In essence it was this experimental model which led Kincaid-Smith to her clinical studies with anticoagulants in glomerulonephritis.

The basic inflammatory agent in Masugi nephritis is probably the antigen antibody complex formed in the glomerulus. The fact that fibrin plays a role in the process was shown by the studies of Silfverskiöld,²⁵ Kleinerman,²⁶ Halpern,²⁷ and Vassalli and McCluskey.²⁸ Using derivatives of heparin or coumadin or both, they were able decidedly to alter the course of the disease. Halpern treated rabbits with heparin and found that the mortality rate in nephrotoxic serum nephritis was reduced from 12 in 18 to 1 in 17. Neither epithelial crescent formation nor scarring of glomeruli, which were present in untreated controls, could be demonstrated by light microscopy in heparin treated animals. By the same token blood urea nitrogen levels were greatly diminished in the heparin treated group.

Although the primary and major effect of heparin is antithrombin, Halpern pointed out that heparin also acts against complement. Since the primary inciting agent for the inflammatory reaction is antigen antibody complex, he raised a question as to whether heparin acted to prevent the combination of antigen antibody complex with complement, thus preventing the inflammatory response. The study of Vassalli and McCluskey²⁸ indicated that it is most likely the anticoagulant activity of heparin rather than its anticomplementary effect which is responsible. They anticoagulated their test animals with warfarin and obtained a result very similar to that of Halpern. Thus, since the action of warfarin is to reduce the amount of circulating prothrombin complex, without affecting complement, the deposition of fibrin is incriminated. They also showed that, even though the kidneys of the treated animals exhibited a minimal inflammatory response, gamma globulin (interpreted as antibody) was found by immunofluorescence in the glomerular basement membrane. It would seem that anticoagulation did not act by preventing deposition of antigen antibody complex, but rather by preventing the deposition of fibrin. Whether the beneficial results are due to

the prevention of fibrin formation within the microcirculation or outside the circulation (that is, the glomerular capsular space and tubules) is a subject for future investigation.

Mural deposition of fibrin in arteries and arterioles. Fibrin is deposited in the walls of arterioles and arteries as well as in the glomerular capillaries in malignant hypertension. It may be deposited acutely or over a long period. It is formed in the vessels that show the characteristic concentric, lamellated hyperplasia of the smooth muscle, sometimes referred to as the "onion peel" appearance. This fact has escaped the attention of most pathologists because it cannot be seen by light microscopy with the conventional histologic stains, but has been clearly demonstrated by use of the immunofluorescent technique of Coons by Gitlin et al²⁹ and Fennell et al.³⁰ These vessels are the hallmark of a rapidly rising blood pressure and this probably represents a leakage of plasma fibrinogen into the interstices of the hyperplastic smooth muscle cells.

This process may be seen in its acute form in the lesion which in the past has been referred to as "fibrinoid necrosis" of the arterial wall. This lesion can be easily detected by ordinary histologic techniques and is often considered a diagnostic criterion for malignant hypertension. It is not a mysteriously derived unknown substance, but simply represents acute damage to the vessel wall with clotting of fibrin following the escape of plasma into the arterial wall.

Lendrum³¹ has shown that in patients with malignant hypertension, small focal deposits of fibrin may be found in glomerular capillaries.

Renal deposition of fibrin has been detected in several types of experimentally induced malignant hypertension. Masson and coworkers³² produced massive glomerular capillary thrombosis by inducing malignant hypertension with angiotensin. Skelton made similar observations with hypertension produced by anabolic steroids.³³ More recently intravascular as well as intramural clotting has been demonstrated in hypertension induced by unilateral nephrectomy, sodium chloride and desoxycorticosterone administration.³⁴ The malignant hypertension was accompanied by fibrin deposition in subendothelial and intramural location in the mesenteric, pancreatic and renal arteries. Fibrin was also found in the glomeruli in the capillary lumens and the mesangial interstices. In addition to the intravascular clotting, a hemo-

lytic anemia which exhibited the red cell changes characteristic of microangiopathic hemolysis developed in these animals.

Intravascular clotting and microangiopathic hemolysis have been demonstrated in malignant hypertension in man as well.^{31,35}

The most likely explanation for the fibrin within the muscular walls of arteries and arterioles is that the increased intraluminal pressure caused by the hypertension distends the vessels and separates endothelial walls and disrupts basement membranes, allowing plasma and red blood cells to escape from the circulation. The exposure of the fibrinogen in the plasma to the tissue thromboplastin of the extravascular environment then causes conversion to fibrin. At the same time the exposure of the basement membrane on the luminal side triggers the clotting mechanism by attracting platelets and activating Hageman factor, resulting in mural and intravascular occlusive thrombi. We have observed the phenomenon in an experimental model of eclampsia.³⁶

In summary, fibrin is deposited in the kidney by a variety of mechanisms. Knowledge of these mechanisms is essential to a rational approach to therapy. It is doubtful that anticoagulant therapy will prove useful in all instances, but it is clearly useful in some and needs considerable experimental and clinical exploration. It is also important to be aware of the fact that agents other than those directed against the clotting mechanism such as phenoxybenzamine (Dibenzylin®) may be useful in preventing the deposition of fibrin in the kidney.

Liver Disease

Hemorrhage is a frequent complication of both acute and chronic hepatic disease. On occasion it is a fatal complication. Upper gastrointestinal tract hemorrhage may be due to mechanical rupture of esophageal varices or to erosion of a blood vessel at the base of a mucosal ulcer in the stomach or duodenum. Some patients have a hemorrhagic diathesis with petechiae and ecchymosis of the skin, particularly at points of trauma.

It has long been recognized that many patients with liver disease have a defect in their blood coagulation mechanism. In the past this has been largely attributed to two causes: (1) diminished synthesis of certain components of the hemostatic mechanism and (2) a rapid, easy activation of the fibrinolytic enzyme system. Recent studies have

demonstrated that disseminated intravascular coagulation must be added to this list.

It may be useful to bear in mind the function of the normal liver. The liver plays an essential role in hemostasis and thrombosis. There are two basic reasons for this: (1) the liver cells synthesize, and release into the blood stream, fibrinogen, prothrombin, Factor v, Factor x and Factor ix, and (2) the Kupfer cells (phagocytic reticuloendothelial cells) rapidly remove substances from the circulating blood which trigger the clotting mechanism, namely thromboplastin³⁷ and colloidal and particulate matter. It has also been claimed that they remove fibrinolysin activator from the circulation.³⁸

The role of the liver in the removal of procoagulant substances from the circulation is well illustrated by the recent studies of Deykin et al.³⁹ Intravenous injection of serum into rabbits resulted in a hypercoagulable state characterized by a shortening of the whole blood clotting time and in the formation of a thrombus in an isolated segment of vein. The procoagulant activity of the serum was dependent on the presence of activated Factors ix and xi in the serum. The thrombotic response was rapidly dissipated in the intact animal. The infusion of serum into the portal vein was less efficient in producing thrombosis and the thrombotic response disappeared more rapidly. When the hepatic circulation was occluded the thrombotic response was prolonged. The importance of the hepatic clearance mechanism was emphasized by the observation that when the circulation to the liver was occluded the rabbits routinely died within 15 minutes. The lethal effect could be prevented by the administration of heparin, indicating that it was caused by disseminated intravascular coagulation. During perfusion of serum through the isolated rabbit liver *in situ*, Factors ix and xi activities were reduced to low levels and the thrombogenic activity of the serum was similarly depressed.

The role of the reticuloendothelial system and of hepatocellular damage in liver disease in man is dependent on the type of damage. In acute hepatocellular change, as in acute yellow atrophy, the major problem is reduced synthesis of fibrinogen and prothrombin complex. However, in cirrhosis, although there may be some reduced synthesis, the major problem is "blockade" of the reticuloendothelial system. "Blockade" of the reticuloendothelial system implies a diminished uptake of par-

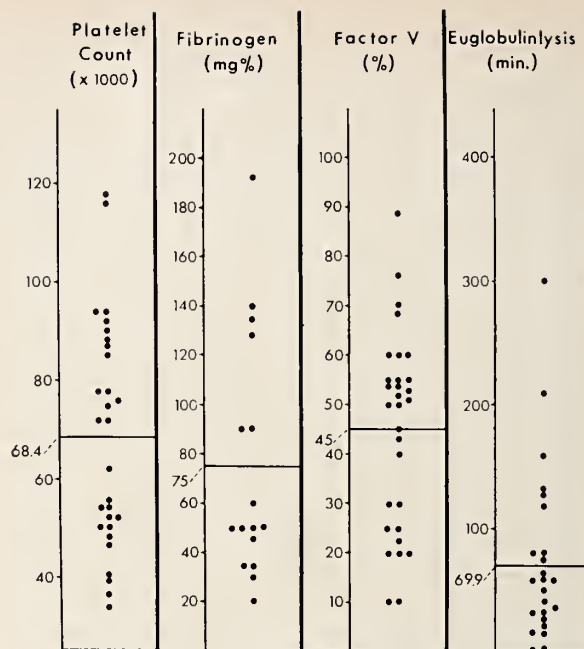


Chart 4.—The low levels of circulating platelets, fibrinogen, Factor v and the evidence of an activated fibrinolytic system are indicative of disseminated intravascular coagulation in these patients. (Courtesy of Dr. M. Hörder⁴² of the Department of Medicine, Justus-Liebig University, Giessen, Germany.)

ticulate matter from the circulating blood. It occurs in a variety of circumstances and can be induced temporarily by exposure of the blood stream to bacterial endotoxin, particulate matter, cortisone and certain fatty acids. In cirrhosis it is probably due to an overload of the Kupfer cells with lipid substances⁴⁰ and to the diversion of blood away from the liver through the collateral shunts that develop.

The first evidence that cirrhosis may be accompanied by disseminated intravascular coagulation came from the study of Johansson.⁴¹ He observed a patient with cirrhosis, a bleeding tendency and a rapidly enlarging tender spleen. Clotting studies revealed the changes characteristic of intravascular coagulation. When heparin was administered to the patient, all the clotting factors returned to normal levels.

A study of Hörder⁴² puts this observation on solid ground. Thirty patients with cirrhosis and portal hypertension had a decided reduction in platelet count, in fibrinogen and in Factor v. The great majority also had an increased fibrinolytic activity (Chart 4). In addition, he gave heparin to one of the patients, with a return to normal of all clotting indices (Chart 5).

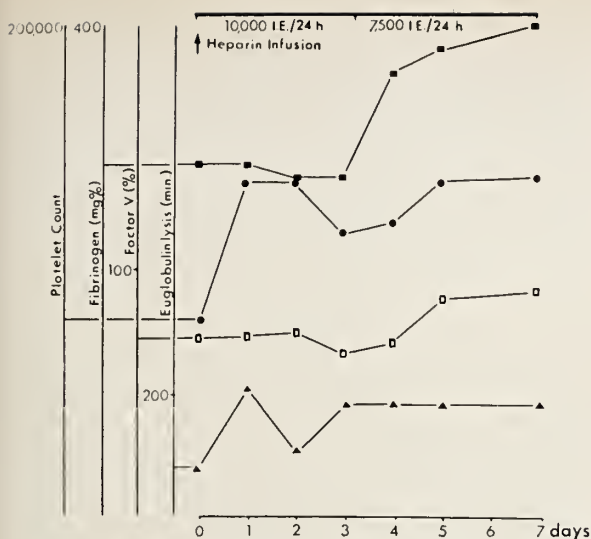


Chart 5.—Heparin administration in cirrhosis of the liver with portal hypertension. (Courtesy of Dr. M. Horder⁴² of the Department of Medicine, Justus-Liebig University, Giessen, Germany.)

Of major interest is the question of where the intravascular clotting occurs in cirrhosis. Pathologic studies have revealed that it is primarily in the portal circulation, but in some cases also in the pulmonary circulation. In 64 of 126 cases (51 percent) of postnecrotic cirrhosis, Hou and McFadzean⁴³ found fresh mural thrombi composed of platelets and fibrin or old fibrin plaques which were the sequelae of previous thrombi. These recent and old thrombi varied from 1 mm to 12 mm in diameter and were found in the portal, splenic and superior mesenteric vein. The clotting in the portal circulation is of the recurrent type and small in amount, and it appears to be the most important site of clotting. Of course, the occasional case of massive thrombosis of portal, splenic or mesenteric vein is well known.

The involvement of the pulmonary circulation by thrombi in cirrhosis is less frequent but is of great interest, since it is associated with pulmonary hypertension.

Many patients with cirrhosis of the liver and portal hypertension exhibit a profound cardio-pulmonary circulatory disturbance. Murray et al,⁴⁴ studying a selected group of 24 patients with cirrhosis, found an increased cardiac output, an increased total blood volume, an increased peripheral blood flow, and an arterial oxygen unsaturation. They interpreted some of these changes as an evidence of shunting of systemic venous blood through pulmonary arteriovenous anastomoses.

Naeye⁴⁵ described five patients with portal hypertension due to cirrhosis and observed the anatomical changes characteristic of pulmonary hypertension. The hearts exhibited right ventricular hypertrophy and dilation. The pulmonary changes varied from moderate arterial intimal proliferation of endothelial cells and fibroblasts to advanced plexiform lesions that resembled recanalized thrombi. Recent emboli or thrombi in varying stages of organization were widespread throughout the small pulmonary vessels.

Portal venous thrombi were found in three of the patients, one of whom had organizing thrombi in collateral varicose esophageal and gastric veins. No other sites of origin for pulmonary emboli were found. The question of the nature of the fibrin deposits in the pulmonary circulation remains problematic. Two possibilities exist: They represent either (1) emboli from the primary thrombotic site in the portal veins, or (2) thrombi arising *de novo* in the lung. The enormously dilated collateral circulation would provide easy access of emboli to the lungs. On the other hand it is equally likely that they are thrombi formed because of the entry of procoagulant substances into the portal circulation from the gastrointestinal tract, substances which ordinarily are removed by the reticuloendothelial system, which is bypassed or "blockaded" in cirrhosis. The thrombi in the pulmonary circulation may be responsible in part for the pulmonary hypertension. A corollary to the concept is the idea that vasoactive amines (such as 5-hydroxytryptamine or tyramine) from the intestinal tract might also add to the pulmonary hypertension.

Whatever the mechanism, intravascular clotting may occur in patients with portal hypertension due to cirrhosis. The clotting is usually small in amount and chronic in duration, but enough to be detectable by studies of the hemostatic medium. In a few patients the pulmonary vascular bed is the site of considerable fibrin deposition.

At the San Francisco General Hospital we have found another cause of acute and massive disseminated intravascular coagulation in cirrhosis, namely Gram-negative bacteremia. A large number of patients with infection of this kind die of endotoxin shock. In these cases bacterial endotoxin is the trigger for the clotting episode. The source of the bacteremia is variable but often it is pneumonitis. The whole process is contributed to by the "blockaded" reticuloendothelial system

which in cirrhosis fails to remove quantities of bacteria that the normal liver could easily handle.

Another possible etiologic factor for intravascular clotting is the effect of the ingestion of alcohol. Lindenbaum and Hargrove⁴⁶ observed ten episodes of thrombocytopenia in five alcoholics with delirium tremens. Platelet counts rapidly returned to normal after ingestion of alcohol was discontinued, and thrombocytosis developed. Further studies are required to determine whether this is a direct or indirect effect of alcohol ingestion, and whether or not the platelet change is accompanied by changes in other clotting factors.

Plague

Plague has been known as a deadly and terrifying disease for at least 2,000 years. Although it is of little concern to a North American physician, it continues as a problem in parts of Asia. Its historical interest for the Western World prompts the inclusion of plague in this review.

In a sense the demonstration by Finegold et al⁴⁷ of disseminated intravascular coagulation in plague is a rediscovery. Glomerular capillary occlusion by fibrin thrombi was found in seven of twenty cases in a Philippine epidemic of plague in 1904 by Herzog.⁴⁸ They were also found in two of twenty-five cases of pneumonic plague from the Manchurian epidemic of 1910-1911,⁴⁹ and in approximately 40 percent of 75 cases of bubonic plague in Manila from 1912 to 1914.⁵⁰ For the past 30 years, the finding has been overlooked by students of plague.

Finegold's contribution was to demonstrate the generalized Shwartzman reaction in experimentally induced pneumonic plague in monkeys. He observed glomerular capillary thrombi in 80 percent of animals dying of the disease induced by pulmonary exposure to *Pasteurella pestis* and in six of seven injected subcutaneously. Glomerular capillary thrombi are the hallmark of disseminated intravascular clotting. The animals apparently died of endotoxin shock, before renal insufficiency became a factor. Studies of the hemostatic mechanism were confirmatory. Prolongation of the clotting time, prothrombin time, and partial thromboplastin time was associated with progressive thrombocytopenia. There was no evidence of a circulating anticoagulant, or of massive activation of the fibrinolytic enzyme.

With the advent of antibiotic therapy, infection with *Pasteurella pestis* has usually been successful-

ly controlled wherever patients have had access to medical facilities. In occasional cases, however, people have died of plague despite successful antibiotic sterilization of their blood and tissues.⁵¹ It is clear that these as well as many patients in antiquity died of endotoxemia with shock and disseminated intravascular coagulation.

(To be continued in October issue.)

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(References to be continued in October issue)

CONSERVATIVE THERAPY FOR HIATAL HERNIA

"I think . . . that hiatal hernia surgery is rarely needed if the patient is treated correctly. In my experience, the proportion of patients with hiatal hernia that have ultimately come to surgery is certainly much less than 5 percent. The indications for surgery . . . have been severe complications, such as stricture, that did not respond to medical therapy or ulceration of the esophagus that ultimately turned into stricture; but more than not I've . . . referred patients for surgery in whom medical therapy has failed. Years ago we talked about intractable ulcer disease and came to realize that this, in most cases, merely represented a posterior penetrating ulcer. In hiatal hernia disease, we do get intractable patients. Most of these I think I can categorize . . . into a psychological group of young women that have been unable to take their antacids and, for one reason or another, have absolutely not responded to medical therapy. In these cases, surgery has been recommended. But again I would state it is infrequently needed."

—LAWRENCE D. WRUBLE, M.D., Memphis
Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 1, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

MEDICAL STAFF CONFERENCE

Atrial Myxoma

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* Today we are presenting our Residential Grand Rounds, an event we look forward to all year. The case for presentation will be discussed by Dr. Richard Dicus, the Chief Medical Resident.

DR. DICUS:† The patient is a 50-year-old white man who first noticed dyspnea on exertion and easy fatigability approximately 12 years ago. In 1958 physical examination and cardiac catheterization data suggested mild mitral stenosis. The left atrium and mitral valve were explored by three surgeons and appeared normal. A biopsy specimen of the atrial appendage was normal. The patient noted some symptomatic improvement after operation and was followed here for three years. He required cardioversion twice during this time, and at his last visit normal sinus rhythm was present. He did not return until 1968, at which time he complained of a re-exacerbation of dyspnea and orthopnea with increasing weakness and fatigability. Examination in July 1968 revealed evidence of mitral regurgitation. There was only a moderate increase in the pulmonary wedge pressure. The symptoms seemed far out of proportion to findings at catheterization. Because of increasing symptoms, the patient was restudied in December 1968, at which time cineangiography was performed.

Dr. Keene will demonstrate the radiographic findings.

DR. KEENE:‡ Chest radiographs made in 1958 showed unmistakable left atrial enlargement, and when the patient returned in 1968 the left atrium was massively enlarged (Figure 1). A cardiac angiographic study was performed. The catheter was introduced in retrograde fashion into the left ventricle. An area of calcification was noted posteriorly in the region of the left atrium. With injection of contrast medium most of the anterior mitral leaflet appeared restricted, simulating the findings seen in ordinary mitral valve stenosis. However, there was enough mitral valve insufficiency to demonstrate a radiolucent, partially calcified mass which filled most of the left atrium.

DR. DICUS: Thank you, Dr. Keene. At operation a massive left atrial myxoma which literally bulged out of the left atrium was removed. This tumor weighed almost 300 grams; it appears to be one of the largest described in the medical literature (Figure 2). The patient has shown considerable improvement in his breathing and exercise tolerance, although atrial fibrillation and the murmur of mitral regurgitation persist. The immediate question raised is, how could we have been so misled in the diagnosis for 10 to 12 years? Knowing the diagnosis, I reviewed the patient's chart and would now like to re-present his medical history.

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†Richard B. Dicus, M.D., Chief Resident in Medicine.

‡Richard J. Keene, M.D., Resident in Radiology and Trainee in Cardiovascular Radiology.



Figure 1.—Chest radiograph taken in 1968 showing enlargement of the left atrium.

Between 1957 and 1958, when symptoms compatible with congestive heart failure first developed, the patient was examined by the same reliable observer three times, and on each occasion distinctly different cardiac findings were noted. The erythrocyte sedimentation rate at that time varied between 25 and 29 mm per hour. The patient was seen here in September 1958, and at that time the cardiac findings were even more divergent. Four examiners described a systolic murmur, nine a diastolic murmur, seven a loud S_1 , and only three an opening snap. As we have heard, the mitral valve was normal at operation. There is an interesting brief note in the patient's chart on the first postoperative day. Apparently acute respiratory distress developed when he was turned on his right side. This was quickly relieved when he resumed the supine position.

Postoperatively, conversion of the cardiac rhythm from atrial fibrillation to normal sinus rhythm was carried out and P mitrale was now quite apparent on the electrocardiogram. While being followed in clinic the patient had an episode of flank pain and hematuria when, presumably, normal sinus rhythm was present, although an electrocardiogram was not taken specifically at that time. In December 1961, the first clear-cut description of a pansystolic murmur was noted.



Figure 2.—Photograph of atrial myxoma removed at operation.

During the next seven years the symptoms progressed, and the patient returned for evaluation. His history at this time included two brief episodes of chest pain, one of which was associated with syncope. During his fourth admission here in July 1968, he had a transient episode of paresthesias of the left face and arm, numbness of the tongue, dizziness and diplopia. There were no obvious neurological abnormalities on examination, and the symptoms quickly disappeared. The erythrocyte sedimentation rate ranged from 44 to 74 mm per hour and the total serum globulin level was 4.2 grams per 100 ml. The cardiac catheterization findings did not explain the degree of the patient's disability. The overall clinical appearance at the time suggested either active rheumatic carditis or cardiomyopathy, perhaps associated with a collagen-vascular disease. I neglected to mention that he also gave a history typical for Raynaud's phenomenon.

Ultimately the definitive diagnostic procedure, cardiac angiography, was carried out. The history as presented has been biased by my foreknowledge of the diagnosis, but the clues were there: variable heart murmurs, systemic emboli, syncope, positional symptoms, unexplained increase in the erythrocyte sedimentation rate, and elevated serum globulin level. The significance of these clues was not appreciated, however, because the possibility of myxoma had not been considered—a dramatic demonstration of the old adage that one must think of the diagnosis in order to make it.

Historical Features

Our frustration in attempting to establish the diagnosis in this patient represents the rule rather than the exception. By 1951 the diagnosis of atrial myxoma had not been made on a living patient, and the classic reviews at that time were written by pathologists, not clinicians.¹ A presumptive clinical diagnosis of myxoma was reported for the first time by Kirkeby and Leren² in 1952. It remained for Steinberg and coworkers³ to make the definitive diagnosis by visualization of the mass with use of cardiac angiography. As it was originally performed through a peripheral vein, this method would now be considered inadequate, especially in most patients with severe pulmonary hypertension and right-sided congestive heart failure. Utilizing cardiopulmonary bypass, Crafoord⁴ was the first to remove successfully such a tumor from the left atrium.

The atrial myxoma was rapidly becoming more than a pathological curiosity, and in 1960 two important reviews regarding the clinical manifestations were published. Aldridge and Greenwood⁵ were stimulated to study this entity because they had made the diagnosis accidentally in the course of mitral valve operations in three instances. (One of the patients died during the first postoperative day.) They had set out to establish criteria which would enable distinction between left atrial myxoma and mitral stenosis. We will hear about their conclusions later. In the same year a study appeared in the *American Heart Journal* which emphasized the histological and histochemical evidence for the neoplastic nature of myxomas, hence refuting the older concept that myxomas originate from degenerated thrombi.⁶ Differding, Gardner and Roe⁷ from this institution reviewed (in 1961) all cases of myxoma removed surgically which had been reported in the literature and added two more cases from this hospital. In 1963 Goodwin⁸ wrote his classic article on the clinical manifestations of left atrial myxoma. He pointed out the very high frequency of systemic manifestations—high erythrocyte sedimentation rate, low grade anemia, fever, weight loss, and increased serum globulins. In 1966 an attempt was made to review all 60 cases of atrial myxoma in which surgical operation had been performed.⁹ This review emphasized two significant points: Two-thirds of left atrial myxomas were diagnosed inadvertently during operation for presumed mitral valve disease, and discovery of the tumor accidentally while the patient

was already on the operating table had a definite bearing on the surgical outcome. In those patients in whom the correct diagnosis was made preoperatively and appropriate preparations made, the survival rate was 83 percent. In those in whom the diagnosis was not made until the left atrium had been opened, the survival rate was only 65 percent. In 1967 Gerbode¹⁰ reported the first known recurrence of a left atrial myxoma after initial resection; we have since seen a recurrence in one patient followed at this hospital. The possibility of recurrence has prompted surgeons to excise a liberal portion of the interatrial septum at the point of attachment of the myxoma.

There have been no systematic follow-up studies of patients with atrial myxoma. The bulk of the medical literature is devoted to case reports, newer and simpler methods of diagnosis (for example, echocardiography and radioisotope scanning) and case reports of unusual cardiac and systemic manifestations.

General Features

Some of the general statistics regarding cardiac myxomas are of interest. The overall incidence of primary cardiac tumors has been estimated to be 0.03 percent. Atrial myxomas represent approximately 50 percent of all primary cardiac tumors. In reviewing the pathology files at this hospital, it is apparent that the myxoma is rarely an incidental finding at autopsy. Perhaps a more pertinent statistic is the frequency of the accidental discovery of myxoma at mitral valve operation—0.5 to 2.0 percent. These tumors are much more common in the left atrium: 75 percent in the left atrium and 25 percent in the right. They are localized specifically to the endocardium surrounding the fossa ovalis. Female patients usually predominate in most series, as is the case for mitral stenosis. The age range is wide, but the 30 to 60 age group is the most common.

Clinical Features

The clinical features of left atrial myxoma have been summarized very well by the cardiac surgical group at Merritt Hospital in Oakland: "These patients walk a tightrope between calamitous systemic embolization, intractable cardiac failure, and sudden death."¹¹ Hence the clinical features can be divided into those related to obstruction of the mitral orifice, to systemic embolization, or to the systemic manifestations.

TABLE 1.—Symptoms and Signs of Atrial Myxoma Related to Obstruction of the Valve Orifice

	Incidence (percent)
Dyspnea	90
Hemoptysis	15
Syncope or vertigo	25
Constant systolic and diastolic murmur	50-65
Constant systolic murmur with inconstant or absent diastolic murmur	15
Constant diastolic murmur with inconstant or absent systolic murmur	25
No murmur	8
Accentuated S ₁	75
Opening snap	5-30
Clinical evidence of pulmonary hypertension	70
Sudden death	15

TABLE 2.—Clinical Manifestations of Left Atrial Myxoma

Incidence of Common Constitutional Manifestations (Percent)		
	Left Atrial Myxoma	Mitral Stenosis
Fever	53	4
Anemia	44	8
Weight loss	35	11
Increased erythrocyte sedimentation rate	70	15
Abnormal serum proteins	50	33
<i>Other Less Common Findings</i>		
Clubbing of fingers	Hypercalcemia	
Splinter hemorrhages	Raynaud's phenomenon	
Hemolytic anemia	Pericardial friction rub	
Thrombocytopenic purpura	Erythrocytosis	
Joint effusions	Asthenia and hyperpigmentation	
Gangrene of acral parts		

The most prominent and debilitating symptoms are related to the obstruction at the mitral orifice or to movement of the pedunculated mass back and forth across the mitral valve or to both these phenomena (Table 1). In this situation the symptoms closely mimic mitral stenosis, and it is apparent that dyspnea both on exertion and paroxysmally is by far the most common complaint. Syncope or vertigo, particularly as related to position, has been reported in as high as 25 percent of patients. The most frequent finding on cardiac examination is a constant systolic and diastolic murmur, which is found in 60 percent of patients. Approximately 25 percent have a constant diastolic murmur with an inconstant or absent systolic murmur, and a small but significant percentage (8 percent) have no discernible murmur. Two other very common findings on cardiac examination are a loud S₁ and clinical evidence of pulmonary hypertension (that is, right ventricular hypertrophy, prominent a waves in the neck veins, or an increased intensity of P₂).^{5,8} The older literature reports a variable incidence of the opening snap. A more descriptive term for this finding is

"tumor plop," as this is now felt to be a noise created by the tumor as it moves through the mitral orifice. This may occur either as the tumor strikes the inside of the ventricular wall or as a result of the sudden tautness in the tumor stalk.

Systemic emboli are alarmingly common, appearing in 35 to 45 percent of patients. Practically all major arterial systems have been reported involved. One important point here is the occasional absence of myxoma tissue in the embolus, since a clot may form on the myxoma with embolization only of the thrombus portion.

A very interesting and as yet unexplained group of symptoms that can be a leading clue to diagnosis is the systemic manifestations: unexplained fever, unexplained anemia, abnormal serum globulins, and an increased erythrocyte sedimentation rate—reported in as high as 70 percent of cases (Table 2). In mitral stenosis without bacterial endocarditis, this constellation of findings is quite uncommon. Other features occasionally reported include Raynaud's phenomenon; warm, tender and swollen joints; hemolytic anemia with a microangiopathic appearance on smear; thrombocytopenia; erythrocytosis; clubbing of the fingers; splinter hemorrhages; acral gangrene; and occasionally a pericardial friction rub.

As helpful as these ancillary findings may be, the real problem is in the differentiation of left atrial myxoma from rheumatic mitral valve disease. Table 3 lists features which help to differentiate the two diseases. The electrocardiogram and routine chest radiograph are usually not helpful in distinguishing the two, for there is usually a good deal of overlap in the basic cardiac rhythm and in appearance of the P waves, and the cardiac silhouette is similar in both. Tumor calcification, so frequently mentioned on routine chest radiograph, is actually not common. We have already discussed the importance of the systemic symptoms and the ancillary laboratory findings. One point to emphasize regarding emboli is their occurrence with myxoma when the patient has a normal sinus rhythm and with mitral valve disease when the patient has atrial fibrillation.

Relentless progressive disability over a short period is often a distinguishing feature in myxoma patients. In mitral stenosis the course is more protracted, and intermittent exacerbations can often be traced to some complication such as arrhythmia, pregnancy or pulmonary infection. The association of symptoms with position change is actual-

TABLE 3.—
*Differentiating Features
Between Atrial Myxoma
and Mitral Valve Disease*

Duration of symptoms	1 to 2 years	7 to 15 years
Course	Progressive worsening without response to therapy	Patients often well maintained on digitalis or diuretics
Syncope/vertigo	Up to 25 percent	Exacerbation correlated with arrhythmia, pregnancy, etc.
Positional symptoms	Helpful, if present	Uncommon
Systemic symptoms	Common	Rare, except for paroxysmal nocturnal dyspnea
Systemic emboli	35 to 45 percent	Rare
Cardiac examination	Atypical features Widely split s_1 Tumor "plop"	9 to 15 percent Opening snap and pre-systolic murmur almost always present
Electrocardiogram	Normal sinus rhythm—85 percent	Atrial fibrillation—40 percent
Radiograph	Tumor calcification	Valvular calcification
Cardiac catheterization	Increased v wave and rapid Y descent in absence of mitral regurgitation	a wave $>$ v wave and slow Y descent

ly not common in atrial myxoma, but it is an important clue if present. In mitral stenosis if the patient has an audible diastolic murmur and the valve is not heavily calcified, an opening snap is almost always present and quite distinct; if normal sinus rhythm is present, there is nearly always a presystolic accentuation. With atrial myxoma these latter findings are infrequent.

At cardiac catheterization the contour of the pulmonary capillary wedge pressure may be helpful. Myxoma patients commonly have a striking v wave and a rapid Y descent, both reminiscent of mitral insufficiency, but this occurs in the absence of other evidence of mitral regurgitation. These findings are quite dissimilar from those in isolated mitral stenosis, where the a wave is usually greater than the v wave and the Y descent is slow. After belaboring the point, I would remind you of the conclusion that Aldrich and Greenwood⁵ reached after their careful review in 1960: "From the analysis it is concluded that differentiation between left atrial myxomas and mitral stenosis is usually impossible."

It is important to emphasize that an absolute distinction at the bedside need not be made but that the clues should be recognized and cardiac angiography carried out. The following clues in the history and physical examination should alert the physician to the possibility of atrial myxoma:

- Absence of history of rheumatic fever or previous heart murmur in a young patient who presents with congestive heart failure and cardiac murmurs.

- Rapid, unexplained progression of pulmonary hypertension.

- Systemic emboli in the absence of atrial fibrillation.

- Progressive left-sided heart failure and unexplained neuropsychological problems.

- Lack of an opening snap or presystolic accentuation in the presence of a loud S_1 and diastolic murmur.

- Disagreement among reliable observers concerning their auscultatory findings.

- Change in murmurs or symptoms with positional changes.

- Persistent unilateral pleural effusion in a patient with presumed mitral stenosis.

- Major systemic manifestations in a patient with presumed mitral valve disease.

- Failure of response to appropriate therapy in a patient with presumed bacterial endocarditis.

Therapeutic Considerations

The efficacy of surgical therapy in this disease is difficult to determine because of lack of adequate follow-up studies; however, I would agree that the surgical prognosis is good if certain principles are followed. For example, if the diagnosis is established before cardiac operation, the patient's prognosis is definitely better. Utilizing open heart procedure, the atrium and tumor are well visualized and, since contractions can be temporarily stopped, there is less risk of embolization during manipulation of the tumor. As mentioned previously, removal of a substantial patch of atrial septum at the site of attachment of the myxoma in hopes of preventing recurrence is becoming a standard procedure. This approach is supported by the findings at pathological examination of scat-

tered foci of myxomatous tissue surrounding, but at some distance from, the point of attachment to the atrial septum.

Experience at UCSF Medical Center

Because of the relative frequency of the disease at this hospital and because of a personal interest, I have reviewed the experience with atrial myxoma

TABLE 4.—Findings in Patients with Left Atrial Myxoma at the University of California Medical Center

<i>Cardiac Examination</i>		<i>Number of Patients</i>
<i>Findings Compatible with:</i>		
Mitral stenosis		2
Mitral insufficiency		2
Mitral stenosis and insufficiency		1
No cardiac abnormality		2
<i>Cardiac Catheterization</i>		
<i>Patient</i>	<i>Mean Wedge Pressure (mm Hg)</i>	<i>Pressure in mm Hg, Systolic/Diastolic</i> <i>Pulmonary Artery Right Ventricle</i>
2	29	64/30 67/6
3	15	31/14 31/8
4	..	68/43 63/16
6	..	42/23 42/7
7	37	98/36 102/14

recorded at the University of California Medical Center. The total number of cases in the pathology files is eight, and in all eight cases the tumor was clinically significant. Antemortem diagnosis was made in seven; in the remaining case, diagnosis was established at postmortem examination. In that case the patient had idiopathic myelofibrosis and died suddenly after an episode of acute pulmonary edema. In the remaining patients the preoperative diagnosis was established by left ventricular angiography in three, by pulmonary angiography in one, by histology of the arterial emboli in two, and accidentally at cardiac operation in one. The left atrium was involved in all eight cases. The initial impression or referring diagnosis at the time of hospital admission included the following: mitral stenosis in two patients, subacute bacterial endocarditis in two, known arterial emboli in two, cardiomyopathy with mitral regurgitation in one (the patient presented today), and myelofibrosis in one. Table 4 represents a consensus of the findings on cardiac examination. Of note is the fact that no cardiac abnormalities were

TABLE 5.—Laboratory Data in Patients with Left Atrial Myxoma at the University of California Medical Center

Patient	Hemoglobin (gm/100ml)	Erythrocyte Sedimentation Rate (mm/hr)	Serum Globulin Level (gm/100 ml)	Body Temperature (C°)	Urinalysis*	Electrocardiogram
1	11.7	38.0	8 to 12 RBC No protein Many granular casts and "cellular" casts	First degree heart block Left atrial abnormality
2	14.5	36	..	37.4	3 to 4 RBC No protein Occasional granular casts	Normal sinus rhythm Left atrial abnormality
3	15.7	56-72	3.8	37.0	..	Atrial fibrillation P mitrale (after cardioversion to normal sinus rhythm)
4	12.4	..	3.4	38.1	1 to 2 Hyaline casts No protein	Normal sinus rhythm Poor R wave progression Borderline abnormal P waves
5	14.0	..	4.8	38.1	4 to 5 RBC 3+ Protein	Normal sinus rhythm Left atrial abnormality
6	11.3	73	3.9	37.5	Rare RBC 1+ Protein	Normal sinus rhythm Left atrial abnormality
7	11.0	70	5.0	38.5	Occasional RBC No protein	Incomplete right bundle branch block Left atrial abnormality

*Findings expressed as red blood cells (RBC) or casts per high power field.

discerned in the two patients who presented with peripheral emboli. Cardiac catheterization (Table 4) was performed in five cases and, when it was obtainable, the wedge pressure was elevated with a rather striking elevation of the v wave. All the patients had mild-to-moderate pulmonary hypertension.

The pertinent laboratory data in these seven cases is summarized in Table 5. In four instances in which the erythrocyte sedimentation rate was measured, there was considerable elevation. In five instances in which the serum globulin level was measured, borderline abnormal or high levels were found. This usually consisted of an elevation of the α_2 and gamma globulin peaks. A low grade fever was noted in four of seven patients, one of whom had endocarditis. Hematuria was found in three patients and proteinuria in two; renal function was normal in these patients. A particularly striking finding was the frequency of abnormal p waves on the electrocardiogram. This included the two patients who presented with arterial emboli and who on physical examination had no detectable cardiac abnormality. In all cases except one, normal sinus rhythm was noted on the electrocardiogram.

In all seven cases the myxoma was removed successfully. However, there was one postoperative death, resulting from Gram-negative pneumonia. There has been one postoperative recurrence; the other five patients have "improved" (subjective improvement of symptoms in four cases and hemodynamic improvement in one patient in whom follow-up catheterization studies were done).

The patient with a recurrence of the myxoma is one of those reported upon in 1961 by Differding, Gardner, and Roe.⁷ This patient initially presented at the age of 12 with bizarre neuropsychological complications for which he was twice referred to the pediatric and metabolic services. No cardiac abnormalities were found and a diagnosis of "periodic hypothalamic dysfunction" was made. Subsequently he had an unexplained episode of profound shock and coma and ultimately an arterial embolus to the leg which was found to be myxomatous. He did well following cardiac operation until six years later when right hemiparesis, aphasia, and athetoid movements suddenly developed. Operation was again performed and a large, pedunculated myxoma was found arising

approximately from the same area as the original tumor.

The pathological findings in the cases in which operation was done are of interest. The smallest and most easily fragmented myxomas were found in the patients who presented with arterial embolization and no cardiac abnormality. All tumors which were attached to a pedicle with some freedom of motion were associated with findings of mitral stenosis on physical examination. The tumor obtained from the patient with subacute bacterial endocarditis showed Gram-positive organisms and inflammatory cells at the base of the myxoma. In the patient with idiopathic myelofibrosis, scattered foci of extramedullary hematopoiesis were found in the myxoma.

In summary, at the University of California Medical Center our experience with atrial myxoma has paralleled that described in the literature—a wide variety of presenting clinical features, heated disagreements as to the physical findings, a variety of approaches in establishing the diagnosis, and finally a generally favorable response to surgical operation. Surgical technique has reached the point where one can be confident of the outcome; however, the diagnosis must be established early. This remains the major challenge.

DR. SMITH: We have time for comments or questions.

DR. MORRELLI: * Have levels of rheumatoid factor been reported in these patients?

DR. DICUS: I know of only two cases in which this was mentioned, and in both cases the rheumatoid titer was normal.

DR. SCHMID: † Why do these patients have systemic manifestations? Have any immunologic studies been performed?

DR. DICUS: There have been some relatively unsophisticated attempts to study the immunologic response of the patient to the tumor. In one case a homogenate of the tumor administered to the patient revealed no evidence of a systemic reaction. This same homogenate was used as a skin test to determine the presence of delayed hypersensitivity. The response to the skin test was negative. Gel diffusion studies have not shown serum antibodies directed against the tumor. The most

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widely accepted explanations for the systemic manifestations are degeneration and necrosis within the tumor, or the presence of unrecognized systemic emboli, or both.

DR. SOKOLOW:* Did you review any of the cases on the vascular surgical service? How often do patients who present with arterial emboli without an obvious cause have myxomas?

DR. DICUS: The pathology files which I reviewed included surgical as well as autopsy specimens, so that all myxomatous emboli would have been included. Besides the two I have already discussed, there was one other case of myxomatous-appearing embolus in the file, and in that case the patient presented with severe peripheral vascular disease and had had many surgical procedures. Tucked away in one of the pathological diagnoses was a comment on the possibility of myxomatous degeneration of a clot or myxoma embolus. When I discovered this, I looked for the patient's chart and found that she is now in the hospital. I have recently examined her and could find no evidence of a cardiac abnormality. The possibility of a myxoma must be looked into more carefully, however.

DR. WILLIAMS:† Would you comment on some of the features of right atrial myxoma?

DR. DICUS: Twenty-five percent of myxomas are found in the right atrium. The differential diagnosis of these tumors includes constrictive

pericarditis, tricuspid stenosis, recurrent pulmonary emboli with pulmonary hypertension, right-sided endocarditis, Ebstein's anomaly and carcinoid heart disease. The typical manifestations of right atrial myxoma include severe right-sided congestive heart failure, most often associated with murmurs of tricuspid valve disease and frequently with pulmonary emboli. In addition, there can be cyanosis and polycythemia due to shunting of blood from the right atrium through a patent foramen ovale into the left side of the heart. The right atrial myxomas are also associated with systemic manifestations such as fever, elevated erythrocyte sedimentation rate, and frequently with pericardial friction rubs.

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Specialty Conferences

Dementia Current Concepts

DISCUSSIONS BY NAZHIYATH VIJAYAN, M.D.,* JOVEN R. CUANANG, M.D.,*
PIERRE M. DREYFUS, M.D.†

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DR. DREYFUS: Dementia — a symptom complex characterized by gradual decline of intellectual function, failing judgment and loss of memory— constitutes a serious medical, social and economic problem. The majority of chronically demented patients are sent to nursing homes or mental institutions for custodial care with a label of “chronic brain syndrome,” often without thorough neurological evaluation. All too frequently dementia is attributed to cerebrovascular disease or to some obscure degenerative process, and treatable diagnostic possibilities are frequently overlooked. Usually once a patient has been committed to a mental institution no further attempts are made to learn more about underlying etiologic or pathophysiological features of the illness. This approach tends to foster an attitude of complete therapeutic nihilism.

Despite the advances in the fields of neurobiology, virology and electron microscopy, very little is known about the causes of dementing illnesses or the process of senescence of the nervous system. Eventually, the causes of these diseases may be discovered, provided diagnostic and investigative

efforts are carried forward with the most sophisticated biophysical, biochemical and virological techniques available. At present, however, these techniques are either not readily available or they remain impractical for purposes of surveying and studying large patient populations. In general, detailed neurological evaluation can rule out most of the medically and surgically remediable dementias. In some cases, a brain biopsy for biochemical, histopathological, electron microscopic and virological studies seems warranted and should be seriously contemplated.

We envisage the day when most chronic forms of dementia will be found to have a readily recognizable metabolic, immunologic or infectious etiologic derivation and consequently will be preventable or treatable.

Dr. Vijayan will now present a case which will serve as focal point for a discussion of current investigative techniques and pathophysiological concepts of certain types of dementia.

DR. VIJAYAN: This 61-year-old, right-handed, white woman was admitted to the Sacramento Medical Center on 6 March 1968. For ten years before admission she had had one or two seizures a year. Although these were usually generalized,

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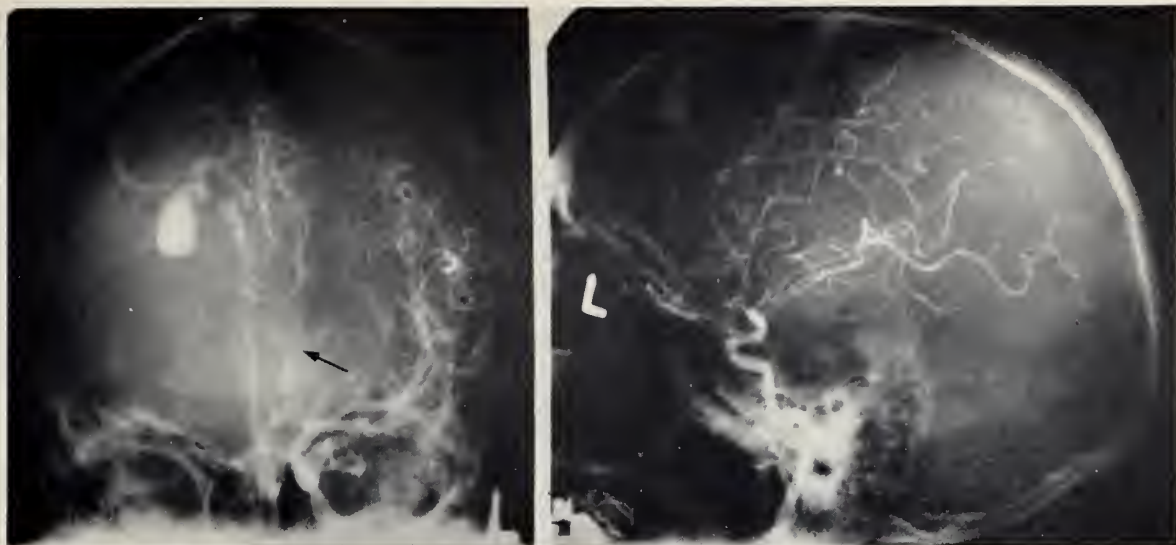


Figure 1.—Left carotid angiogram showing a large arteriovenous anomaly in the right frontal lobe. Note the large, abnormal dilated vessels which fill rapidly from the left carotid artery. Shift of the anterior cerebral artery to the left is also noted.

they tended to involve the left side to the greatest extent. On three occasions the patient was found in an unconscious state, this condition lasting for a period of one hour each time. She was treated with anticonvulsants without receiving much benefit. In the early spring of 1968, the patient began to have severe generalized headaches. She gradually became withdrawn, uncommunicative and disoriented, and on several occasions did not recognize her grandchildren.

Investigation that was carried on while she was a patient at another hospital revealed that she had a right frontal lobe arteriovenous anomaly (Figure 1). Upon transfer to the Sacramento Medical Center, she was fully conscious but mute and uncommunicative. Except for mild left-sided hyperreflexia, no focal neurological signs were elicited. On 12 March 1968 a right frontal hematoma and the arteriovenous anomaly were removed. Following this, she improved, becoming more communicative and able to talk intelligently. At this time, a lumbar puncture showed an opening pressure of 115 mm of water. The fluid contained no cells and had a normal protein content. A month later, following an episode of urinary tract infection and high fever, the patient once again became mute and at times drowsy. Repeated angiographic study revealed no abnormality. The patient continued to deteriorate. She slept much of the time except for short, transient periods during which she would speak a few words unexpectedly and

spontaneously. On 11 June 1968 spinal fluid pressure was 60 mm of water, protein content was normal and no cells were seen. An electroencephalogram revealed generalized theta activity with bifrontal and right anterior temporal delta waves. An echoencephalogram showed no displacement of midline structures. At this stage, the patient had to be fed by tube and was unable to communicate, although at times she appeared to be wide awake with eyes open. She did not respond to either verbal or written commands, although she occasionally vocalized unintelligible words spontaneously. Two lumbar punctures, performed on 14 and 17 June, revealed a pressure of 140 mm and 155 mm respectively.

The patient was seen on our service for the first time on 14 September. Pronounced generalized muscle wasting and inability to respond to verbal commands were noted.

Blood pressure was 140/80 mm of mercury and pulse rate was 120 beats per minute. No abnormalities were noted on examination of the heart, lungs and abdomen. All pulses were strong. No bruit could be heard over the head or neck.

The eyes were conjugately deviated to the left but moved in all directions on doll's head maneuver. There was mild horizontal nystagmus with a rapid component to the left. Pupils measured 3 mm, were equal and reactive to light. Fundi were normal. Mild left central facial weakness was present. The patient blinked at loud noises. She

would forcibly close her jaws when an attempt was made to open her mouth, and she could open her mouth, lick her lips, put out her tongue and swallow spontaneously.

She winced on painful stimulation of either side and she groped with the right hand to protect herself. Motor power could not be assessed but the



Figure 2.—Left carotid angiogram performed in September of 1968, showing pronounced bowing of the anterior cerebral artery. Operative clips are seen under the calvarium.

patient moved all four extremities. Deep tendon reflexes were more active on the left. Plantar response was extensor on the left only. All four extremities were hypertonic. Gegenhalten and a grasp reflex were greater on the left. A prominent snout reflex was elicited. The patient was incontinent of urine and feces.

A carotid angiogram revealed lateral displacement of the thalamostriate veins bilaterally and exaggerated bowing and stretching of the anterior cerebral artery (Figure 2) indicating ventricular enlargement. A pneumoencephalogram showed generalized dilatation of the ventricles (Figure 3). No air could be seen over the convexity of the brain. A radioactive iodinated serum albumin (RISA) scan revealed the characteristic pattern of communicating hydrocephalus (Figure 4).

On 1 October a ventriculo-atrial shunt* using a low pressure Pudenz valve was performed. Two days later the patient appeared to be more alert. The next day she demonstrated purposeful movements on the left for the first time in six months. On the sixteenth post-operative day, she spoke a few intelligible and appropriate words. From then on, she showed steady improvement, being able to communicate with other patients and the staff. She began to recall events of the past and was able to

*In this procedure one of the lateral ventricles is drained into the left cardiac atrium by means of a tube. The valve regulates flow of cerebrospinal fluid.



Figure 3.—Pneumoencephalogram performed in September of 1968—brow-up, left lateral view and frontal view showing pronounced dilatation of the frontal horns of the lateral ventricles.

feed herself. She became continent of urine and feces and was able to walk with support. She was discharged from the hospital in May of 1969 and is at present undergoing a program of rehabilitation.

DR. DREYFUS: Thank you, Dr. Vijayan. Would you care to make a few comments about this most interesting case of reversible dementia?

DR. VIJAYAN: This patient represents a classical example of so-called low pressure hydrocephalus. The generalized seizures with left-sided preponderance which the patient had for about ten years must have been caused by the arteriovenous anomaly embedded in the right frontal lobe. Repeated episodes of bleeding may have led to headaches and the eventual mild left hemiparesis. Excision of the arteriovenous anomaly and the hematoma was followed by definite clinical improvement. The gradual deterioration, a month after operation, characterized by akinetic mutism, bilateral frontal lobe signs and urinary incontinence, can be attributed to the development of communicating hydrocephalus with normal or low pressure. This state was confirmed by means of contrast studies and the RISA scan. The ventriculoatrial shunt was followed by gradual improvement.

At the time of our consultation, the differential diagnosis lay between bilateral frontal lobe disease secondary to surgical operation and repeated episodes of hemorrhage and communicating hydrocephalus. The following points were evidence against the former diagnosis: (1) The patient improved for a period of a month following operation; (2) bilateral frontal lobe signs developed despite the fact that only the right side of the brain was affected by the arteriovenous anomaly; and (3) a generalized disorder of awareness, which could not be accounted for by frontal lobe disease alone, also developed. The studies confirmed our clinical diagnosis of communicating hydrocephalus.

Low or normal pressure hydrocephalus occurs as a complication of subarachnoid hemorrhage, head trauma or chronic meningitis of bacterial or fungal origin. In some patients, no specific cause can be found. In this patient, communicating hydrocephalus undoubtedly developed as a consequence of repeated episodes of subarachnoid hemorrhage engendered by the arteriovenous anomaly.

DR. DREYFUS: Dr. Vijayan, could you discuss the entity of low or normal pressure hydrocephalus?

Low or Normal Pressure Hydrocephalus

DR. VIJAYAN: Derangement in the formation, flow or absorption of cerebrospinal fluid can lead to hydrocephalus. The most common of these three mechanisms is the obstruction to flow. Classically, hydrocephalus is divided into two types, noncommunicating and communicating. In the former condition, the obstruction to flow is proximal to the foramina of the fourth ventricle, and in the latter the obstruction is distal. In either case, excess fluid accumulates since it cannot reach the main sites of absorption. This accumulation increases the intra-ventricular pressure which, in turn, leads to ventricular dilatation.

"Hydrocephalus ex-vacuo" is a separate entity, denoting ventricular enlargement secondary to generalized cerebral atrophy. In this condition, even though there is an excess of cerebrospinal fluid, the fluid takes up the space left by the atrophic brain without causing an elevation of pressure.

A few years ago, Hakim and Adams^{1,2} described a group of patients in whom ventricular dilatation was evident in the presence of normal cerebrospinal fluid pressure and in the absence of cortical atrophy. These patients were found to have a type of communicating hydrocephalus with obstruction situated in the subarachnoid space around the pons and the midbrain. The clinical manifestations of this condition are remarkably characteristic—namely, progressive dementia, bilateral frontal lobe signs, gait disturbance and urinary incontinence. Reduction in the ventricular pressure by means of a ventriculo-atrial shunt is followed by dramatic clinical improvement and reduction in the size of the ventricles. One can be certain that in these cases, normal cerebrospinal fluid (CSF) pressure acts as a dilating force, as evidenced by the facts that the ventricles return to normal size upon reduction of pressure to below normal by the shunting procedure and, neurones and veins near the ependyma exhibit the effects of pressure, being flattened in a plane perpendicular to the lines of force. The mechanism leading to hydrocephalus of this type, in the presence of normal pressure, has not yet been fully elucidated.

It is conceivable that in this condition there is an intermittent increase in pressure which goes unnoticed and may cause the increase in size of

the ventricles. The absence of papilledema in these patients and the normal ventricular and spinal subarachnoid pressures recorded by Hakim¹ in three patients during a 24-hour period provide evidence against this contention. Errors resulting from faulty measuring techniques, although possible, seem fairly well excluded.

Attempts have been made to explain the process of ventricular dilatation in these patients using Pascal's law as it applies to fluids in semi-solid containers. According to this law, the force (F) exerted by fluid on the wall of its container is equal to the pressure (P) times the area (A) on which it acts ($F=PA$). P remaining constant, an increase in the area (A), that is, the ventricular size, can enhance the effective force (F) on the walls of the ventricles. Hakim and Adams^{1,2} contend that initially there is an elevation of CSF pressure due to defective absorption. This leads to an accumulation of CSF and ventricular dilatation. Gradually, equilibrium is reached between CSF production and absorption, the elasticity of the brain is overcome, the ventricles enlarge and the pressure drops to normal or low levels. These authors propose that, according to Pascal's law, normal or low pressure can still exert greater force on the ventricular wall because of an increase in its surface area. This force in turn prevents the ventricles from returning to their original size. An active obliterative process in the subarachnoid cisterns will lead to further reduction in CSF absorption, and ventricular dilatation progresses even in the presence of normal pressure. The anterior horns of the lateral ventricles, being the widest part of the ventricular system, usually undergo maximal dilatation. Because of the large surface area of the anterior horns, the force acting upon the surrounding tissue is proportionately greater. Although this explanation appears to be logical and reasonable, it fails to take into account such important factors as the elastic properties of brain tissue, the complex nature of CSF production and reabsorption and the numerous factors which influence the hydrodynamics of the ventricular system.

Recently, Geschwind³ advanced further hypothetical considerations. He contends that the "hydraulic press" effect postulated by Hakim does not take into consideration the structural properties of the container — that is, the cerebral tissue. Geschwind considers these properties to be the most important factors in the production of ven-

tricular dilatation. Alterations in the pulsatile forces of the choroid plexus may be partially responsible for differential expansion of the ventricles. According to Geschwind,³ a high gradient of pressure between the ventricles and the subarachnoid space cannot account for ventricular dilatation since the subarachnoid space is relatively small and would soon be obliterated by enlarging ventricles. At the moment, very little is known regarding the structural properties of brain tissue.

RISA Scanning

DR. DREYFUS: A number of diagnostic procedures were used in the evaluation of the patient presented by Dr. Vijayan. The angiogram and the pneumoencephalogram revealed the presence of enlarged ventricles. Neither of these procedures can shed light on the hydrodynamic state of the cerebrospinal fluid. In recent years, the use of radioactive iodinated serum albumin (RISA) scanning has been found to be of particular value in this area. Here I^{131} labeled albumin can be introduced with impunity into the lumbar or cisternal subarachnoid space and its flow can be observed at regular intervals by means of an external scanning device. In a normal brain when 100 microcuries of RISA are instilled into the lumbar subarachnoid space and the head is scanned at four hours, the tracer substance which normally accumulates in the basal cisterns gives the scan pattern a "butterfly" shaped appearance (Figure 4). By 24 hours, the isotope has passed anteriorly and laterally over the convexity of the cerebral hemispheres toward the superior sagittal sinus, where it concentrates maximally. By 48 hours, the material has almost completely cleared the subarachnoid space, having been absorbed into the vessels. Additional information regarding clearance of the tracer from the subarachnoid space can be obtained by periodic sampling of blood and determination of radioactivity.

The RISA scan is helpful in differentiating communicating from non-communicating types of hydrocephalus. A different but characteristic pattern is seen in cases of normal or low pressure hydrocephalus. In those circumstances, the isotope tends to accumulate inside the ventricles and virtually none is seen in the basal cisterns (Figure 4). At 24 and 48 hours, the isotope continues to fill the ventricles. This pattern may persist for several days. The material gradually diffuses through the brain. This pattern of flow indicates that cerebro-

spinal fluid cannot circulate through the basal cisterns or over the convexity of the hemispheres. In cases of partial or incomplete obstruction of the ventricular system, some of the material may fill the basal cisterns, where it remains for 48 to 72 hours. In hydrocephalus ex-vacuo, the RISA scan assumes a normal pattern.

In general, RISA scanning yields more information and is technically simpler and safer than is pneumoencephalography which may cause a worsening in the patient's state of awareness. RISA scanning is also useful in postoperative assessment of the efficacy of ventriculo-atrial shunts.

Another procedure which may prove useful in establishing the diagnosis of communicating hydrocephalus has recently been described by Katzman⁴ and his group. This test, called the "flush test," measures the capacity to absorb additional cerebrospinal fluid following the constant and steady infusion of sterile normal saline solution or artificial CSF into the lumbar subarachnoid space by means of an infusion pump, while pressure is being monitored. In normal circumstances CSF absorption is approximately three to four times the amount formed per minute and the infusion of saline solution results in only a slight increase

TABLE 1.—*Treatable Forms of Dementia*

Hypothyroidism	
Nutritional Deficiency:	Pernicious anemia
	Pellagra
	Korsakoff's syndrome
Bromidism	
Electrolyte imbalance	
Hypercalcemia	
Inappropriate antidiuretic hormone secretion	
Cushing's disease	
Neurosyphilis	
Chronic subdural hematoma	
Hydrocephalus — high, normal or low pressure	
Brain tumor	
Wilson's disease	
Chronic liver disease	

TABLE 2.—*Untreatable Forms of Dementia*

Alzheimer's disease
Vascular disease
Pick's disease
Creutzfeldt-Jakob's disease
Huntington's chorea
Demyelinating diseases
Lipid storage diseases
Parkinson's disease
Amyotrophic lateral sclerosis
Viral encephalopathies

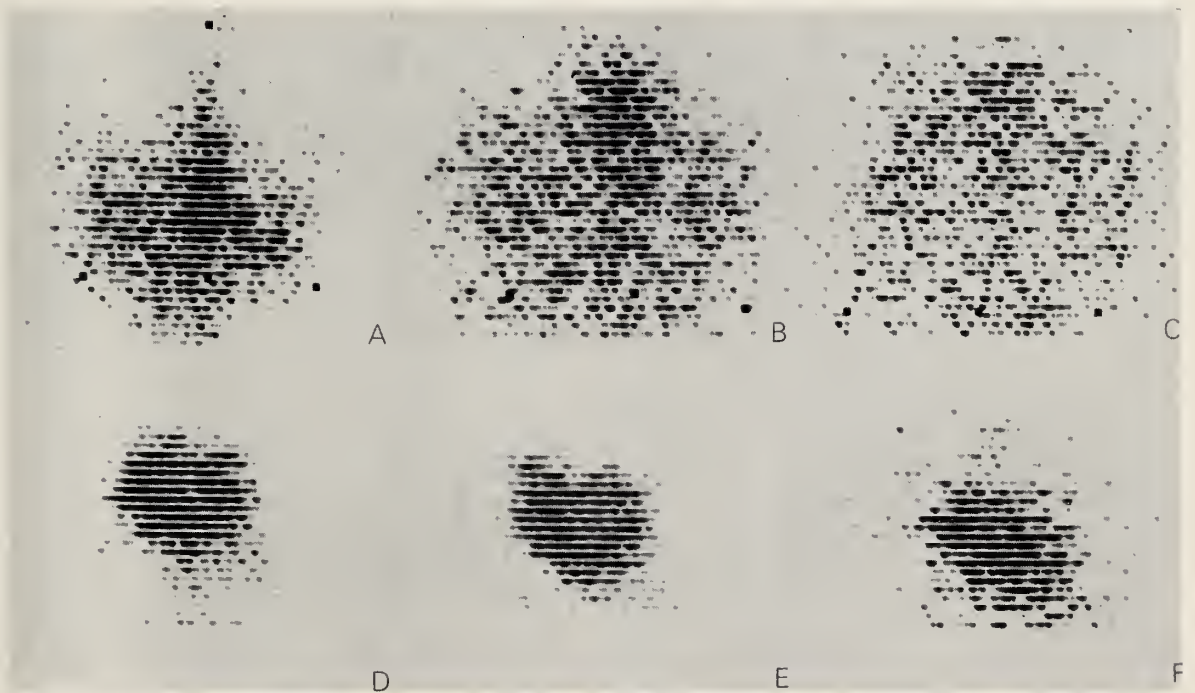


Figure 4.—Radioactive iodinated serum albumin (RISA) scan. Top row, *normal pattern*: A=4 hours, B=24 hours, and C=48 hours after lumbar injection of the tracer substance. Bottom row: Scan in patient with communicating hydrocephalus at 4, 24 and 48 hours. Note difference in pattern and delay in clearance of the isotope.

in pressure. In cases of faulty resorption, such as in communicating hydrocephalus, the pressure rises rapidly to high levels following the infusion of small amounts of fluid.

The case which Dr. Vijayan presented and discussed represents a unique form of treatable dementia. It might be appropriate at this point to discuss other common forms of dementia, some of which are treatable. Dr. Cuanang, will you briefly review for us the causes of dementia and emphasize which forms are treatable or partially reversible?

Differential Diagnosis of Dementia

DR. CUANANG: To review all known forms of dementia would be too time-consuming. It is important, however, to emphasize that many diseases which may have dementia as their major symptom are either completely or partially reversible, especially when recognized early. For the sake of convenience, I have listed these disorders (Tables 1 and 2), separating those for which treatment is available from those which are as yet untreatable. Amongst diseases listed in the first category, a greater number have a metabolic basis and dementia is one of many other clinical features. In the second category, dementia is the principal feature, though it may be part of a generalized neurological disease.

Alzheimer's disease is probably the most common form of dementia encountered. It is usually considered to be a presenile disease having its onset between the ages of 40 and 60. Occasionally, the disease begins as early as the third decade of life. Dementia occurring in the aged (senile dementia) in most instances also proves to be Alzheimer's disease. A survey of approximately 200 brains obtained in a large state institution⁵ revealed that the pathological attributes of the presenile and senile form of Alzheimer's disease are the same—loss of neurons, neurofibrillary tangles and senile plaques in the major association areas of the cerebral cortex. Etiologically and pathophysiologically senile and presenile dementia are most likely identical, the only difference being that they occur in different age groups. Certain predisposing factors may account for qualitative and quantitative differences noted between the older and the younger age groups. The disease has a familial tendency in the latter. Pick's disease, which is pathologically different from Alzheimer's disease, cannot be distinguished from it clinically.

Creutzfeldt-Jakob's disease is a rapidly fatal presenile encephalopathy characterized by dementia; widespread and massive myoclonic jerks in the early stages of the disease are followed by the appearance of other variable neurological symptoms and signs.

Dementia occurring in aged patients is frequently and erroneously; labeled "chronic brain syndrome associated with arteriosclerosis," despite evidence suggesting that only in a small number of patients can vascular disease or stroke be invoked as an etiological factor. Recently, Paulsen and Perrine⁶ summarized their analysis of 30 demented patients in whom this diagnosis had been made clinically. Bilateral carotid angiograms revealed only four cases of either unilateral or bilateral carotid artery occlusion and one case of chronic subdural hematoma. Minor abnormalities of the carotid artery, such as stenosis, kinking or marked tortuosity, were found in 19 patients. A survey by the same authors of 166 cases of proven carotid artery disease revealed only nine patients in whom dementia was the initial or major clinical manifestation. In almost every instance severe focal neurological signs were more apparent than were mental changes. Dementia or confusion was rarely found in patients below the age of 45; these symptoms were somewhat more common in patients over 70 years of age.

Dementia as part of a neurological symptom complex such as hemiplegia, grasping, lack of spontaneity, urinary incontinence, steppage gait and pathological crying and laughing may be seen in the so-called "lacunar state." This pathologic entity is characterized by small infarcts, measuring a few millimeters, spread throughout the cerebral parts of the brain (basal ganglia, thalamus, internal capsule and brain stem) caused by fibrinoid-arteriosclerotic changes seen as a consequence of hypertension or diabetes. The course of the disease is usually of an episodic, step by step nature. Dementia may also be seen following infarction of the "watershed areas" or "borderzones" which are the territories of the brain where the supply of one major cerebral vessel flows into the area of another. Sudden hemodynamic and other changes such as hypoxia, hypotension or increased blood viscosity may precipitate this type of vascular insufficiency and infarction. The clinical course tends to be abrupt and sudden, rather than slow and progressive.

Current Concepts of Dementia

DR. DREYFUS: Finally, we should make a few remarks concerning the etiology of untreatable forms of dementing illnesses. The most common pathological attributes which underly the large majority of dementias is the fallout of cerebral neurones, the loss of normal cortical cytoarchitecture and a compensatory glial reaction. The basic pathophysiological mechanism and the speed with which the disease process progresses vary. Recent advances in neurobiology may provide possible clues to the pathogenesis of some dementing illnesses. It appears likely that a number of disease states hitherto labeled as "degenerative" or "toxic" actually are of viral origin. Recently, Gibbs and his colleagues⁷ were able to identify a progressive encephalopathy in a chimpanzee, 13 months following the intracerebral and intravenous inoculation of homogenized, buffered, surgical biopsy material obtained from the brain of a patient who had Creutzfeldt-Jakob's disease. The clinical findings and pathological changes noted in the chimpanzee bore great similarities to those found in the human disease. These observations have been repeated in two other transfers of the disease from human to animal, and transfer of the illness from one animal to another has also been achieved. The results of investigations strongly suggest that this disease is caused by a transmissible agent, possibly a virus. So far, none has been isolated. Slow or latent viruses are suspected to be responsible for such neurological diseases associated with dementia as Parkinson's disease and amyotrophic lateral sclerosis. It is conceivable that other forms of dementia such as Alzheimer's or Pick's disease may be of viral origin. Therefore, it is important to study such patients thoroughly, including the carrying out of viral studies on material taken from the brain for biopsy or obtained at postmortem examination.

Biochemical studies on cerebral tissue obtained from patients with Alzheimer's and Creutzfeldt-Jakob's disease have been undertaken in a number of laboratories. The results obtained reflect in a subtle way what one is able to see under the microscope — neuronal loss, mild demyelination and glial proliferation. Unfortunately, they do not point to any specific metabolic aberration. In Alzheimer's disease, recent data⁸ suggest an alteration in protein synthesis and an accumulation of acid polysaccharides. In Creutzfeldt-Jakob's dis-

ease, a decrease of ribonucleic acid in the cell has been noted in the cerebral cortex. This change is accompanied by a reduction in protein and ganglioside (neuronal lipid) concentrations.⁹ One might conclude that the decrease in ribonucleic acid could be due to the fact that a virus, after gaining entry into the cells, has effectively interfered with the formation of polyribosomes, subcellular organelles.

Electronmicroscopic examination of biopsy and postmortem material obtained from patients with dementing illnesses has failed so far to provide etiologic elucidation. No viral particles have been identified in any of the diseases studied. However, of particular interest are the changes in the neuronal fibrous proteins noted in cases of Alzheimer's disease.¹⁰ Normal neurons examined with the electronmicroscope are found to have microtubular structures about their nuclei which stream out into the cell's processes. These microtubules are composed of globular protein molecules or subunits which determine the characteristic morphologic features of the tubule by their mode of aggregation. Very little is known concerning the function of these presumably vital structures or organelles. It is postulated that microtubular or fibrous proteins are concerned with the movement of products synthesized near the nucleus which flow down the axon to synaptic terminals and out into the dendrites—axoplasmic and dendritic flow. The transported substances most likely subserve a transmitter or neurosecretory function vital to the operation of the neuron. These substances are affected by agents known to inhibit the mitotic spindle (podophyllotoxin, vincristine, vinblastine). In cases of Alzheimer's disease, the microtubules or fibrous proteins are twisted and distorted. This abnormality has also been observed in cases of postencephalitic Parkinson's disease. It is postulated that a small modification in the composition of the microtubule protein could alter the geometry of the protein subunit polymerization and thus give rise to twisted tubules. Conceivably, a slow virus could bring about this structural defect. Effective therapy for viral disorders may soon become available and as a consequence hitherto untreatable dementias may become treatable or arrestable. Much remains to be done in this group of diseases. Investigations to date hold out hope that the results of these efforts will find useful clinical application.

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THE USE OF LIDOCAINE IN SEVERE CHEST PAIN

"[If you are called to the home of a patient with severe chest pain and a lot of irritability,] you can at least act safely on the assumption that this is ventricular premature irritability. Or let's put it this way—ventricular irritability is the worst thing a patient could be having at this particular time; if it's atrial irritability, there's not much difference. You can act to suppress the irritability by giving a bolus of lidocaine. If the patient has a slow heart rate, you certainly would not want to give any antiarrhythmic drug blindly without knowing for certain just what was going on. If the patient is hypotensive, it would be unwise to give . . . an antiarrhythmic agent without being in a position to control further hypotension should it arise. . . . But in other individuals with infarction, if there is quite a bit of irritability, I would definitely go ahead and give a bolus of lidocaine. . . . Clearly, we want to suppress VPC's in patients with myocardial infarction. . . . The usual dose of lidocaine given blindly intravenously is roughly 1 mg per kg—somewhere between 50 and 90 mg in the average adult—given rapidly."

—ROMAN DESANCTIS, M.D., Boston

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The Health of the Nation's Health Care System

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THIS NATION is faced with a breakdown in the delivery of health care unless immediate concerted action is taken by government and the private sector. Expansion of private and public financing for health services has created a demand for services far in excess of the capacity of our health system to respond. The result is a crippling inflation in medical costs causing vast increases in government health expenditures for little return, raising private health insurance premiums and reducing the purchasing power of the health dollar of our citizens.

As examples of the situation inherited by this Administration: Medical costs are rising at more than double the increase in the cost of living. Physicians' fees, which were increasing at a rate of about 3 percent a year up until 1965, have since the introduction of Medicare and Medicaid been rising at 6 percent a year. The expense of one day's stay in a hospital, not including a physician's care, has gone from \$44 in 1965 to \$70 today, and will probably be \$80 next year. Within three years at the present rate of inflation, hospital expense will hit \$100 a day. The Medicaid program is costing two and a half billion dollars a year in Federal funds alone, more than double the estimates made at the time of its passage.

Badly conceived and badly organized, the Medicaid program has attempted to provide medical services for the poor by pushing them into the nation's already overburdened health care system without developing the capacity in the

system to serve them and without building the capability in the states to manage the program. As a result, by 1975 at the present rate of increase, Federal costs for Medicaid could go as high as \$12 billion per year with the states paying an additional \$12 billion. And this on top of a Federal expenditure for health which today is larger than the entire budgets of each of the Departments of Agriculture, Commerce, Housing and Urban Development, Interior, Justice, Labor, Post Office, State, Transportation and Veterans Administration. The Federal health budget in fact now exceeds the total national budget of all but eight nations in the world.

Our overtaxed health resources are being wastefully utilized, and we are not adding to them fast enough to keep pace with rising demand. Our health priorities are critically out of balance. Our incentive systems all lead to overuse of high-cost acute-care facilities, while the need increasingly is for lower-cost alternatives. We emphasize spectacular achievements in the healing arts, but have given too little attention to the prevention and early care of illness, which must be the first line of attack on our health problems.

Faced with this extremely difficult situation, we nevertheless cannot abandon our national goal of effective and dignified health care for every American no matter what his station in life or where he lives. We cannot accept anything less in this the most affluent society in the world. As long as there are people in this country who are denied essential health services because of poverty, or race, or lack of access for any reason, we have fallen short of our promise as a Nation.

*This report was a general release dated 10 July 1969. It is printed here because of its significance and timeliness. Dr. Egeberg's appointment now has been confirmed.

Our task now as a nation is to acknowledge the extreme urgency of the situation, to take certain steps to arrest the inflation that is paralyzing us, and to put into motion initiatives that ultimately will reshape the system. This task is obviously not one for government alone, although government has a major role to play. Much of the burden must be taken up by the private sector since it has the primary responsibility for the delivery of health care. Unless government and our vast array of private institutions can learn to work together we cannot succeed. The fault in the past has been shared by both. Too often government has operated independently, and even blindly. Medicaid was launched without adequate preparation, with a staff of only 80 people to manage \$2½ billion in expenditures, and with no provision for expansion in the nation's capacity to meet the increased demand for health services thus created. And too often the private sector has been reluctant to give up outmoded practices that are unsuited to the incredibly rapid changes of our society—to new demands, and increased demands.

This Administration is committed to correcting these past failures of government, and to challenging the private sector to begin the process of revolutionary change in medical care systems. To this end we are taking the following administrative and legislative actions:

- We are eliminating the allowance to hospitals and nursing homes for unidentified costs;
- We are enforcing regulations limiting payment to individual practitioners under Medicaid;
- We are increasing reviews of drug utilization, drug pricing, drug efficacy and safety;
- We are directing the Public Health Service to promote alternative medical care facilities;
- We are requiring tighter, more frequent reviews of hospital care for patients;
- We are requiring that physicians be identified by Social Security number in all Medicare and Medicaid transactions in order to assist in the audit and review of those transactions.
- To help alleviate a serious manpower shortage, we are establishing an Office of New Careers with the top priority of developing programs for returning Vietnam medical corpsmen;
- We are proposing legislation under Medicare and Medicaid to bar from participation practitioners who have consistently abused the program; to gain greater flexibility to engage in incentive

reimbursement and demonstration projects; to withhold reimbursement for facility expenses incurred contrary to regional or local plan for health care facilities; and to insure that government does not pay more for services than the charges to the public at large;

- We propose to shift emphasis of the Hill-Burton hospital construction program to the development of facilities for preventive care, outpatient care, and to the modernization of inner-city hospitals;

- We will move in the direction of reducing the Medicaid burden on general revenues by shifting to various forms of prepayment;

- We are establishing a Secretary's Task Force on Medicaid and Related Programs under the leadership of Under Secretary John Veneman and Mr. Walter J. McNerney, to deal immediately with the crisis in that program. This work group will

- a. develop and recommend utilization review procedures, incentive reimbursement methods, and standards for medical care;
- b. develop procedures for better determining eligibility for medical and public assistance, to aid the states to simplify eligibility determinations, and to develop methods for more accurately predicting costs; and
- c. develop a stronger administration on the Federal level, to aid states and localities to better control their programs, and to develop technologies of medical assistance management.

These steps will insure that the Federal Government gets more for its health dollar. But the major portion of the health care dollar is not spent by government. It is spent by and on behalf of private consumers through voluntary insurance and personal expenditures in the private sector. Millions and millions of health care transactions occur every day in which the determining factors are utilization and pricing decisions made by private individuals, by physicians and other professional persons, by industry and labor and by voluntary institutions. Neither government decision nor government review is a determining factor in these transactions.

We must insure that the private consumers in these actions receive adequate services at a reasonable price. This requires a major commitment by the varied segments in the private health care

industry to drastic changes in the industry. To this end, we will ask national, state and local organizations to assume new responsibility for leadership in promoting such change. A good part of the job is theirs to do, and with great urgency.

In particular:

- We will ask and challenge the health insurance industry, including non-profit insurers, to mobilize itself to expand coverages to additional groups, to provide broader and more effective coverage, to change their coverage to encourage preventive services to provide incentives to keep people out of hospitals and other high cost facilities, and to play an active role in monitoring the excessive use of scarce facilities, such as hospital beds;

- We will ask and challenge the physicians, dentists, and other practitioners of the nation through the national societies, and through the county associations, to establish procedures to review the utilization by their members of various services; to review in particular the use of nursing homes which now absorb one-third of the \$5 billion expended on Medicaid by Federal and state governments; to encourage utilization by their members in all instances of less expensive types of care; and to discipline those who are involved in abuses;

- We will ask and challenge the hospitals of the nation through their boards of trustees, their administrators, and their organized medical staffs, to review and revise their procedures for admissions and discharges so that no patient stays longer in an acute facility or long-term facility than is absolutely necessary; and we will ask them to work with other hospitals in the community to promote management efficiency, to share equipment and services, and to reduce the unnecessary duplication of facilities;

- We will ask and challenge the deans and faculties of the medical schools and all who are involved in the education and training of professional manpower to find new ways to expand the number of persons they are training, to shorten the time needed for training and to orient their training more towards the immediate needs of the country, such as comprehensive medical care for the poor and near poor;

- We will call upon the governors and state legislatures to reexamine and evaluate the role of state health departments in improving the delivery of health services and to review state requirements for licensing and certification which stand in the way of the proper use of scarce manpower;

- We will demand of ourselves and the Federal Government, in general, that we put our own house in order, including reviewing the role and performance of Federal hospitals, Federal health programs, and the future of the Commissioned Corps of the Public Health Service;

- We will call upon citizens' groups and consumer organizations to continue their efforts to hold the medical care industry and government responsible for good management and for constructive policies in delivery and pricing of services;

- We will ask and challenge American business to involve itself in the health care industry, including the creation of new and competitive forms of organization to deliver comprehensive health services on a large scale in what has been up to now largely a cottage industry;

- We are creating a special industry group under the chairmanship of Mr. David J. Mahoney, president of Norton Simon, Inc., to develop and stimulate industry programs to provide health education and preventive health care for employees at every level and their families.

Over the coming months we will call together each of these groups to hear what they propose and to learn what they will expect of us in return. Many dedicated persons among them are already working towards these goals. We have much to learn from them. What we will ask of all is that their efforts be greatly broadened and intensified.

This country has made achievements in the quality of care beyond anything that could have been imagined at the turn of this century. It is that very success that has brought us to the present test of whether we have the capacity to extend that same quality of care to all in society at a price which they can afford. What is ultimately at stake is the pluralistic, independent, voluntary nature of our health care system. We will lose it to pressures for monolithic government-dominated medical care unless we can make that system work for everyone in this nation.

Preventive Medicine—Present and Future

WILLIAM H. STEWART, M.D., *Washington, D.C.*

MY ASSIGNMENT HERE is to talk about Preventive Medicine—Present and Future. We can take the past of preventive medicine as stipulated. The evidence of its success is clearly demonstrated in the lengthened lifespan, the decline and fall of many communicable diseases, the dominance of chronic and degenerative disease as health problems in the American population today. All of these are twentieth century developments, and all are attributable in very large measure to preventive medicine.

Looking honestly at the present, we have to acknowledge that preventive medicine is in a state of partial eclipse—to use an astronomical image appropriate to a nation of armchair astronauts. For the past half century, and especially in the two decades since World War II, medicine has been in a therapeutic era. The accent has been on diagnosis, treatment and cure. The glamor fields have been those associated with cure and repair, like surgery and chemotherapy.

None of us would deny the brilliant accomplishments of this period. Millions are alive and healthy today who would have been doomed to premature death or lifelong disability without the great advances of therapeutic medicine and the swift progress of biomedical research on which those advances have been based. Moreover, it is evident that this progress will continue as we exploit our knowledge and technology further.

We need to recognize, however, that this progress has been purchased at a price. The thrust of biomedical science has required specialization. Specialization in turn has led to compartmentalized knowledge and, to a great extent, to compartmentalized medical education and compartmentalized practice. Almost inevitably, our concern with the human being has been fragmented. And he, after all, is the purpose of the whole endeavor.

In effect, the person has become the object

rather than the subject. The individual has been placed outside the system, and in order to enter it he must submit himself as an object for depersonalized attention. It sometimes seems that he is being asked to shed his community, his family, and his “self” in the process, so that the physician can get down to the piece of the action he is mainly interested in.

In my view the revolutionary change needed in our health system is to reorient it to the human being. The individual, as a person, should be the center around which the service system revolves, his total state of health, its measure of success or failure.

Some group within the medical field needs to generate the force that will bring about this change. This is a role that I believe preventive medicine is particularly well qualified to play.

This role will require a substantial change of orientation for preventive medicine. I have the impression that both educators and practitioners in this field, involved in a climate of specialization and fragmentation, have been seeking to define and defend a clean-cut, discrete specialized fragment of subject matter, to have and to hold. What I am suggesting would reject this approach. You would substitute for it a concern with the totality of the medical experience as it affects the whole individual.

A year or so ago I came across an eloquent statement by Dr. Gerald Besson, president of a county medical society here in California, which places the medical experience in a total context. Let me quote a couple of paragraphs for you:

“The environment’s hazards are physical, biological, or socio-cultural. Our defenses are genetic, learned, or involve external assistance. The bulk of the interaction between self and environment takes place without medical care intervention. Indeed, it is only a minute segment of this endless encounter that involves medical care. Much of the interaction may be influenced in favor of the host by certain acts by either the individual—if he knows how—or by a professional. . . .

Dr. Stewart was Surgeon General, Public Health Service, U.S. Department of Health, Education, and Welfare, Washington, D.C.

Presented before the Section on Preventive Medicine and Public Health at the 98th Annual Session of the California Medical Association, Los Angeles, March 15 to 19, 1969.

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"In the framework of this definition the profession changes its emphasis. We deal more with people and less with patients. We deal more with health than with disease. We deal more with the human condition, less with formalin-fixed pathology. We deal more with the socio-cultural hazards than with the biological ones. We deal more with a continuum of care, less with the episode of sickness."

A New Definition of "Preventive"

In my judgment Dr. Besson has outlined a compelling argument for the primacy of preventive medicine. But making it work will require a new definition of "preventive" and a new depth of involvement with man's total environment.

In the past, preventive medicine, in partnership with the disciplines of public health, has achieved outstanding successes by concentrating on prevention of specific diseases. The prevention we are talking about now is preventing the disintegration of the individual. We need to give priority not only to the postponement of death and the prevention of specific disabilities but also to prevention of deviations from the norm that interfere with individual fulfillment.

In short, we shall be altering and enlarging the traditional concept of prevention—which is essentially a negative concept—into a concept of health maintenance and health advancement. We shall be looking toward the individual who is not simply un-sick but truly healthy — equipped physically, emotionally and socially to handle his interactions with his environment.

This transition will require us to adapt some of our traditional tools and develop new ones.

The science of epidemiology, for example, has been one of our proudest ornaments and greatest contributions. It will have instant application to this new challenge, but in a somewhat modified form. Now, in addition to studying the circumstances associated with disease, we shall be applying the same discipline to the circumstances of health.

Clearly, the characterization of health in terms of microbiology and infectious disease epidemiology cannot serve as the total base for our future endeavors. Rather, the moving tides of society, which we have helped to move, are compelling us to redefine our purposes in quite different terms—the terms of man's adaptation to his total environment.

Immediately we find ourselves on dark and shaky ground. This new definition of purpose rests on sciences much less comfortably exact than microbiology. We find the familiar equations of one cause—one disease disappearing into a complex of multiple causation. We confront new sets of interactions among interlocking environments. We are dealing with the internal environment of the human being, affected by the stresses and strains of physical, social and psychological surroundings. These surroundings are increasingly subject to man's collective control. A newly oriented discipline of preventive medicine can help guide society toward exercising such control for the benefit of the healthy individual human being.

Control of Genetic Defects

Consider, for example, the remarkable number of avenues now being opened up by biomedical research which point toward prevention and control of congenital defects. In this single and critically important field we find the interplay of man's internal and external environments. In fact the National Foundation has recently estimated that some 20 percent of all birth defects are genetically determined; another 20 percent are believed due to external environmental factors; and the remaining 60 percent are probably due to the interaction of genetic and environmental influences before birth.

Among the environmental factors are included not only the drugs and medications a mother may take during her pregnancy, but also the infections she may contract—infections stemming from viruses such as cytomegalovirus, herpes simplex, mumps, chickenpox, smallpox, vaccinia and rubella.

We were all shocked to learn that the 1964-65 rubella epidemic was responsible for the birth defects found in some 20,000 to 40,000 infants. This dramatic episode tends to obscure the fact that rubella takes a toll in loss of life, mental retardation and body defects every year, although on a smaller scale. We are also now beginning to suspect that damage to the fetus may occur in larger numbers beyond that first trimester than was originally believed. And we must be impressed by the estimate that at least 4 percent of institutionalized children are there because of defects attributed to rubella.

Now, thanks to a chain reaction of scientific and technological successes, we are on the threshold

of preventing and perhaps ultimately eliminating this toll. A simple, fast and reliable test for rubella immunity is already in being. Now the challenge before us is one we are thoroughly familiar with—using the preventive tools so that all who need them receive their benefits.

The rubella story is the most immediate but by no means the only example of new scientific knowledge in the birth defects field. The collaborative perinatal research project initiated by the National Institutes of Health almost ten years ago, although by no means completed, is yielding important results.

For example, it now appears almost certain that the brain alterations of many severe retarded may have been caused by an injury—such as a compression of the umbilical cord—which reduces the blood-oxygen flow to the brain during gestation. Further, it has been discovered that long-term, partial oxygen deprivation during gestation—rather than sudden, total deprivation—produces the types of cerebral palsy seen in humans.

In addition to the severe and prolonged hypoglycemia in childhood—which has been confirmed as a cause of cerebral palsy and mental retardation—it has been found that some hypoglycemic children are sensitive to the amino acid leucine. Since this variety of the disease often clusters in families and often improves spontaneously between ages three and six, the value of special diets becomes even more apparent as a method of preventing permanent brain damage during those crucial years.

A number of metabolic and enzymatic disorders appear to be closely related to defects apparent at birth and to those which become evident in later life. Among research results in these fields is a relatively simple, inexpensive test for cystic fibrosis, a hereditary disease that formerly caused death for many of its victims before the age of two. Now, with easy diagnosis possible, and subsequent appropriate use of antibiotics, nutritional therapy and mechanical devices, the life expectancy of many of these children has been extended to adulthood.

Research is under way to determine the impact of malnutrition in the causation of birth defects. Research projects on the cytogenetics of mongolism and other chromosomal defects are seeking to elucidate which chromosomes are responsible for specific aspects of human development—suggesting a future in which we may be able to repair or engineer a specific gene structure.

We all realize that mental retardation is a multifaceted problem with medical, psychological, educational, and social components. Perhaps the one area that has received least attention in relation to its importance is the social science field—an area that obviously can contribute significantly to the well-being of the mentally retarded individual and his family. In order to narrow the gap in our knowledge of the sociological and other aspects of mental retardation, the National Institutes of Health last year held the first of a series of conferences on the role of social sciences in mental retardation research. The group discussed family components in mental retardation, family relationships of institutionalized and non-institutionalized retarded children, family theory as it relates to mental retardation.

This has been a very quick skimming of the surface of a single field of inquiry which is furnishing grist for the mills of preventive medicine. It is, to be sure, a field of enormous significance, with an awesome claim on our attention. Each year some 500,000 fetal deaths are associated with birth defects; another 62,000 deaths between the ages of 1 and 19 are attributed to the same cause; and by conservative estimate there are 15 million persons in the United States today with one or more congenital defects which affect their daily lives—and the lives of their families and communities.

The External Environment

Turning to man's external environment, we find again new worlds to be explored and eventually conquered, in which preventive medicine can play a leading part—and indeed must, if the job is to be done.

The threat of noise, to cite a single example, involves both a definable degree of physical insult resulting in specific physical disabilities and a less precisely definable but no less important insult to the quality of the life we lead. We already have a solid base of knowledge, almost entirely related to occupational exposures, which demonstrates that noise causes hearing loss. We know that noise can cause physiological changes, including cardiovascular, glandular and respiratory effects reflective of a stress reaction. We know that a high proportion of machinery in use in certain industries produces noise levels that are potentially harmful.

But we have not yet extended our observations outward into the community where people live—to the world of jackhammers and power mowers

and booming hi-fi sets and screeching airplanes that we call home. We need to look ahead just a few years to the awesome potential of the Supersonic Transport Age. We need to find out, before it happens, whether or not we may find ourselves existing in a coast-to-coast drop-forge foundry, to borrow a phrase from Senator Proxmire of Wisconsin.

Wide Horizon, High Ceiling

What I am really saying is that the horizon of preventive medicine is as wide and its ceiling as high as we want them to be. The sky's the limit, and we really "ain't seen nothing yet."

It is heartening to note, in looking toward the future, that a new blue-ribbon advisory body under the chairmanship of former HEW Secretary Arthur Flemming has recently been appointed to advise on goals and priorities in the preventive medicine field. This Secretary's Advisory Committee on Health Protection and Disease Prevention, which has a two-year charter, could well signalize a new emphasis and a new ascendancy.

More than 50 years ago—in 1916, to be precise — Dr. William H. Welch and Mr. Wickliffe Rose described public health and preventive medicine in these terms:

"The field covered by the terms 'hygiene,' 'sanitary science,' 'public health,' 'preventive medicine' is so broad and varied that it is hardly possible within a brief compass to indicate all of the subjects here included. Strictly speaking, the territory

embraces a group of sciences or the application of various underlying sciences. Unity is to be found rather in the end to be accomplished—the preservation and improvement of health — than in the means essential to this end. It is focusing upon this definite purpose which gives coherence to the organized body of knowledge embraced under the designations 'hygiene' and 'sanitation,' and make important its study and cultivation as a professional pursuit."

One sentence in that remarkable passage presents us the key to understanding the success of preventive medicine and public health in the past. If we use it, that same key will unlock the door to the future. "Unity is to be found rather in the end to be accomplished — the preservation and improvement of health — than in the means essential to this end." That is a statement fit for inscription over any portal — educational, governmental or professional.

In the intervening years our means have multiplied. Our perception of the end has changed—for few would have dared, in 1916, to imagine the high level of health to which we can now aspire. But the unity of our effort is still to be found in the preservation and improvement of health of the whole man, the individual in his family and community setting. This is the purpose to which preventive medicine has always been committed and from which it can draw sustenance for a new series of successes.

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EDITORIAL

Disseminated Intravascular Coagulation: New Bottles For An Old Wine

SCARCELY A CLINICAL JOURNAL is published, nowadays, without an article or two ascribing some fresh disorder to inadvertent intravascular coagulation. The appealing view that many apparently diverse pathologic processes have a common basis in diffuse thrombosis within small blood vessels has a lusty champion in McKay, whose review appears elsewhere in this issue.

Like all new ideas, the concept that disseminated intravascular coagulation is an important pathologic process has its origins in the distant past. As early as 1834, de Blainville¹ demonstrated that the intravenous injection of brain tissue led immediately to lethal, massive intravascular clotting. A half century later, Woolridge² observed that animals would survive if the infusion of tissue extract was sufficiently slow; indeed, no gross intravascular clots could be found. For some time after the infusion, the animals' blood was incoagulable, and further infusions of tissue extracts were harmless. Mills³ and others showed that the blood in such animals would not clot because it was depleted of fibrinogen. In modern terms, the tissues used in these various experiments furnished tissue thromboplastin which activated the extrinsic pathway of thrombin formation and, in this way, initiated clotting within the animals' blood stream. In agreement with this view, clotting factors other than fibrinogen have been found to be depleted (or "consumed") after the infusion of tissue extracts. Antihemophilic factor (Factor

viii),⁴ proaccelerin (Factor v),⁵ prothrombin (Factor ii)⁵ and platelets⁶ disappear most rapidly, changes resembling those which take place when blood clots in a test tube. In addition, deficiencies of Christmas factor (Factor ix), Stuart factor (Factor x) and Factor vii may be detected.⁷ At the same time, the plasma acquires inhibitory activity retarding the formation of a fibrin clot⁸ and, inconstantly, fibrinolytic activity. Defibrination can also be brought about by the injection of thrombin⁹ or certain snake venoms.¹⁰

In animals subjected to sublethal infusions of clot-promoting agents, few if any thrombi are found, even under the microscope. Two hypotheses have been proposed to explain this paradox. Perhaps the clots which form are promptly lysed by plasmin. This fibrinolytic enzyme is activated from its precursor, plasminogen, with particular facility if fibrin is present.¹¹ Were this true, the blood stream should contain degradation products of the digested fibrin. These products could readily account for the concomitant retarded formation of fibrin for, in the test tube, they inhibit the action of thrombin and interfere with the polymerization of fibrin.^{12,13} Alternatively, the formation of fibrin initiated by the infusion of procoagulant substances might be incomplete. Conceivably, the first products of clotting, monomeric units of fibrin, perhaps polymerized with fibrinogen itself, might be readily removed from the blood stream before they had a chance to form macroscopic clots.^{14,15} In support of this, material resembling fibrin has been found in reticuloendothelial cells after the infusion of clot-promoting agents. Of course, these hypotheses are not mutually exclusive, nor can one be certain that the fibrin ingested by macrophages has not already been lysed by plasmin.

Two clinical syndromes have been delineated

which seem to be the counterpart of these animal studies. In *amniotic fluid embolism*, amniotic fluid enters the maternal blood stream during parturition, as proved by the presence of fetal epithelial cells and hairs within the mother's blood vessels. In patients who survive the immediate effects of this disaster, a severe hemorrhagic tendency ensues, characterized by hypofibrinogenemia, thrombocytopenia, the appearance of thrombin-inhibitory and fibrinolytic activity in plasma, and other coagulative defects.¹⁶ It is attractive to think that in this disorder the blood has been clotted within the maternal blood vessels by amniotic fluid or its contaminants. Similarly, *envenomation* by the bite of certain snakes may defibrinate the victim. When the venom is primarily a procoagulant, like that of the Malayan pit viper, the patient may survive the episode without difficulty, just as the patient with congenital afibrinogenemia will not bleed unless subjected to injury.¹⁷ The benign results of this defibrination have suggested the use of snake venoms in the treatment of thrombotic states.¹⁸

In contrast to these two disorders, evidence that other pathologic processes are accompanied by intravascular coagulation rests upon indirect arguments varying in their cogency. Perhaps the clearest example is the hemorrhagic state which follows *massive transfusion of incompatible blood*, recalling to mind that one of the tissue extracts used in Woolridge's classic experiments was erythrocytic stroma. Under these conditions, hypofibrinogenemia and other clotting defects are often detectable.¹⁹ Similarly, Schneider²⁰ attributed the defibrination which may complicate *premature separation of the placenta* to intravascular coagulation induced by the entrance of thromboplastic agents derived from decidua. Although alternative explanations of the hypofibrinogenemia seen in this condition have been offered, one can defibrinate an animal by the infusion of placental tissue.²¹ On shakier grounds, the hypofibrinogenemia sometimes seen in patients with *carcinoma of the prostate*,²² *leukemia*²³ or other *neoplasms* has been attributed to entrance into the blood stream of procoagulant substances derived from the tumor tissues. The same logic may account for the striking hypofibrinogenemia which may complicate severe sepsis. When afibrinogenemia was first detected in a case of *septic abortion*, this state was attributed to a failure of synthesis because coincidentally massive hepatic necrosis was pres-

ent.²⁴ Subsequently, it became apparent that in this syndrome fibrinogen is consumed intravascularly through activation of the blood clotting mechanisms.²⁵ But this syndrome cannot yet be attributed to any bacterial product; perhaps the source of the procoagulant introduced into the patient's blood stream is her own damaged tissue. Similarly, severe hypofibrinogenemia and other clotting abnormalities have been discovered in some patients with *Waterhouse-Friderichsen syndrome*,²⁶ whether caused by the meningococcus or pneumococcus. Gross evidences of intravascular clotting are also to be found in *purpura fulminans*, a peculiarly unpleasant disease in which large patches of gangrene, usually superficial in nature, suddenly appear out of the blue, often some days after a streptococcal infection.²⁷ In this disorder, widespread vasculitis and thrombosis of small blood vessels can be demonstrated, suggesting once again that the procoagulant is derived from the patient's own damaged tissues.

Three advances led to the concept that still other pathologic states might induce widespread intravascular coagulation, perhaps insufficient in itself to cause significant hypofibrinogenemia but adequate to bring about ischemic damage. First, Merskey²⁸ and others demonstrated material immunologically like fibrin in the *serum* of persons who had apparently undergone intravascular coagulation. Presumably, this material either was fibrin which had been degraded by plasmin or was soluble, incompletely clotted fibrin. Were such "fibrin degradation products" to be found in other conditions, one might postulate that intravascular coagulation had taken place even though hypofibrinogenemia could not be detected. Second, Brain and his associates²⁹ showed that the red blood cells were severely damaged and took on a characteristic appearance as the result of experimental intravascular coagulation. The cells resembled those of *microangiopathic hemolytic anemia*, a state seen preeminently in *thrombotic thrombocytopenic purpura*, suggesting that in these states intravascular coagulation had occurred. Further, their experiments fortified the view that intravascular coagulation can be brought about by vascular damage, and that the hemolytic anemia which often accompanies such states may reflect physical damage to the erythrocytes as they are caught in the meshes of a fibrin clot. Here are the beginnings of an explanation for the syndrome of violent hemolytic anemia, thrombocyto-

penia and clotting abnormalities observed, for example, in some patients with *eclampsia*.³⁰ Finally, Little³¹ found that he was able to halt the advance of purpura fulminans by the therapeutic administration of heparin, inferring that this disease was, as seemed apparent, the result of widespread intravascular coagulation. This observation has led to the belief that a favorable response to therapy with heparin is evidence that hypofibrinogenemia is due to intravascular coagulation. A striking example is the correction of hypofibrinogenemia which follows the use of heparin in women in whom there has been *intrauterine retention of a dead fetus*.³² Although heparin has not always been helpful in disorders thought to be associated with intravascular clotting, its use is much more logical than that of epsilon aminocaproic acid, an agent which may compound the patient's difficulties by preventing lysis of thrombi.

Consideration of these three criteria has led to the view that disseminated intravascular coagulation plays an important part in such syndromes as *thrombotic thrombocytopenic purpura*, *renal cortical necrosis*, *malignant hypertension*, *cirrhosis of the liver*, *hyaline membrane disease*, *hemolytic-uremic syndrome* and *shock* due to a variety of mechanisms. McKay's review furnishes strong evidence in support of this hypothesis. We are only beginning to appreciate the role of more localized clotting in the *rejection of organ grafts*. And, turning cart before horse, Linton and his colleagues³³ now suggest that the *malignant phase of hypertensive disease* is secondary to renal changes brought about by the deposition of fibrin in renal vascular walls, a truly malignant sequel to intravascular coagulation. Perhaps, too, as Duguid³⁴ believes, Rokitsansky's view that *atherosclerosis* is secondary to fibrin deposition in vascular endothelium is correct. We seem to have come a long way from de Blainville, yet we are only at the beginning of our understanding of the processes of intravascular coagulation and, as always, it is hard to see the future.

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Dementia

INTELLECTUAL DETERIORATION, which may result from a number of disorders, is denoted by the term *dementia*. Difficulty with the clinical characterization of intellect detracts from the precision of the term, but it is the best we have. Memory impairment is a constant feature of dementing syndromes; also present in greater or lesser degrees are loss of the capacity to learn new material and to solve problems, reduction in calculating ability, disturbances in abstract thinking and in the appreciation of visual-spatial relationships. This syndrome is distinct from the reduction of awareness, perception and attentiveness, which is usually designated as *obtundation* or *sensorial clouding*. It is useful to keep these two kinds of confusional states separate because the causes are different (although there is some overlap and profoundly demented patients may appear to be obtunded). "Confusion," then, refers to either of these two kinds of disturbances of mentation, and the term should be avoided for the sake of clarity.

Semantic difficulties have been made no easier by the persistence of the term *dementia praecox*. It came from Morel, a mid-nineteenth century Belgian psychiatrist, who observed an adolescent patient, originally bright and active, as he gradually became gloomy and withdrawn. Unfortunately, and inaccurately, Morel described the patient's illness as a dementia (*praecox*), instead of as the psychotic disorder which we today classify as schizophrenia.

In a specialty conference published in this issue of CALIFORNIA MEDICINE, Vijayan, Cuanang, and Dreyfus from the faculty of the University of California School of Medicine at Davis draw attention to the remediable dementing illnesses. That such catastrophic disorders can be cured deserves emphasis. Moreover, there are several of these treatable disorders that sometimes first come to attention with dementia as the sole clinical manifestation of disease. This group includes hypothyroidism, neurosyphilis, pernicious anemia, chronic subdural hematoma, brain tumor (subfrontal meningioma, in particular), bromidism and other drug intoxications, pellagra, and normal pressure hydrocephalus. The absence of certain physical signs does not exclude any of these possibilities; for example, hypothyroid dementia ("myxedema madness") may occur in the absence

of any other clinical signs of myxedema.¹ Careful exclusion of such disorders by appropriate laboratory and radiological examinations should be carried out in patients with unexplained dementia; advanced age is not always the correct explanation.

Senile or presenile dementia, as pointed out at the UC Davis conference, usually proves to be Alzheimer's disease at post-mortem examination and not cerebral arteriosclerosis. This observation is no small matter in deciding which direction to take in searching out the cause of this disabling disorder.

One approach toward a better understanding of the pathophysiology of the dementias has been the study of overall cerebral blood flow (CBF) and oxygen consumption (CMRO₂) in man. In general, the results of such studies have shown that, whatever the age of the patient at onset, both CBF and CMRO₂ are reduced proportionally with the degree of dementia.² However, there is still no definitive evidence to indicate which is the primary change: (1) a reduction in cerebral blood flow leading to cerebral hypoxia, tissue damage and a reduced cerebral metabolic rate or (2) a primary parenchymatous alteration in the brain manifested by a reduced cerebral metabolic rate followed by a secondary readjustment of the circulation to the reduced metabolic demand of the tissues. There is some experimental evidence to indicate that in senile dementia, circulatory changes are primary,³ while the neuropathological evidence, as alluded to above, is quite to the contrary.

One of the problems in the metabolic assessment of human brain *in vivo* is that the brain is far from being a homogeneous organ; it is simply not like muscle or liver in this respect. If one studies the overall metabolism of an organ whose function as well as structure is clearly compartmentalized, how are the results to be assessed? This problem has been underlined by the recent findings of greatly reduced CBF and CMRO₂ in Wernicke's encephalopathy,⁴ a cerebral disorder in which the anatomical defect is confined to relatively small, circumscribed areas of the diencephalon, midbrain and cerebellum. If the sites of pathologic changes are clues to the localization of metabolic defects in disease states of the nervous system, then the fairly localized metabolic defects in Wernicke's disease may result in a striking reduction of cerebral blood flow and metabolism.

Thus, the measurement of overall cerebral functions can provide general information about disease, but is a seriously limited approach.

Regional cerebral studies are, at present, almost entirely limited to experimental animals; but such studies may be clinically relevant. The following is an example: Hepatic, or portal-systemic, encephalopathy is a disorder in which dementia may be prominent, and in which there is also a reduction of CBF and CMRO₂. Studies of cerebral high-energy phosphates during experimental ammonia intoxication⁵ (a reasonable model for the clinical disorder) have revealed a selective decrease in both adenosine triphosphate and phosphocreatine in basal areas of the brain. These findings correlate well with the clinical syndrome of hepatic encephalopathy, which has features referable to basal ganglia dysfunction. The point is, of course, that the biochemical mechanisms of cerebral dysfunction are likely to be compartmentalized, and this kind of approach to other experimental models of neurological disorders is needed.

Finally, a word about the heterogeneity of the dementias. Korsakoff's psychosis is clinically manifest by a disturbance, often profound, of retentive memory, with all other components of mentation practically intact; confabulation, inconsistently present, appears to be a reaction to this mnemonic failure. Patients with Korsakoff's psychosis may attain a normal score on tests of intelligence, provided they can keep the problems in mind long enough to formulate an answer. Certainly this disorder is as different from Alzheimer's disease as the settings in which the two disorders arise. For the purpose of arriving at a correct bedside diagnosis, it is useful to lump together the dementing disorders. On the other hand, it appears likely that progress in the basic clarification of these conditions will be made by considering them quite separately.

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Bridging the Generation Gap— A Progress Note

ALMOST A YEAR AGO a new program "Bridging the Generation Gap" was launched through these columns. A progress report now seems in order. The purpose was to strengthen communication and understanding between the student and practicing generations of California physicians. The instrumentality to accomplish this was a subscription to CALIFORNIA MEDICINE bought for a medical student by a practicing physician. The recipient could be a medical student known to the doctor or one whose name was picked at random. In either case the names of the donor and donee were each made known to the other.

There was a considerable response and a considerable number of person-to-person bridges were established. There is no question that this personal interest was appreciated by those students lucky enough to be the beneficiaries. "Bridging the Generation Gap" also caught the imagination of the Woman's Auxiliary, which has made \$1,200 available to the Council through the California Medical Education and Research Foundation (CMERF) for this purpose. And at its last meeting the Council voted to establish a special rate of four dollars for a student subscription to CALIFORNIA MEDICINE, which doubles the reach of the program.

The overall result will be that something less than 600 students in California's eight medical schools, or about one-fifth of their aggregate student body, will have been reached. Experience indicates that most medical students are surprisingly uninformed or misinformed about many of the worthwhile accomplishments and goals of the practicing profession they are soon to join, as are many practitioners about the ideals, accomplishments and goals of today's students who will very soon be of the profession.

As in medical practice itself, the approach must be personalized. Why not build yourself a bridge, or a number of bridges, across the generation gap in medicine?

Medicine and New Cultural Values

An Editorial Essay

THERE IS ABUNDANT evidence that many long accepted cultural values with respect to what is good, moral or right are now being seriously questioned in our society. We see this happening with respect to the law, the military, the church and the educational enterprise, all of which were established as cultural institutions with responsibility to define, defend, interpret and perpetuate what is deemed to be right and good. These established institutions now seem to be increasingly on notice that they must justify the relevance of their values in today's world or risk losing the support of modern society. Although the spotlight is often on the youthful activists the process is tolerated and often aided and abetted by a kind of tacit public acquiescence which at times seems quite unprecedented.

The thesis of this essay is that this reexamination of traditional values is occurring for very understandable reasons, and that a significant result may be that medicine will take its place among the important arbiters of the new values which are certain to emerge in what will surely be a far more biologically oriented society.

It is suggested that the analysis begin by acknowledging the very real success of the industrial revolution, particularly as it has been accomplished in this nation. This success can be measured by the fairly recent appearance of what might be called critical masses of machinery to do physical work, of mechanisms for instant communication, and of millions of human beings who are the beneficiaries of these achievements. The development of a critical mass of mechanical power now frees men from much if not most of their physical labor. A critical mass of virtually instant communication greatly increases the sensitivity and awareness of enormous numbers of people in a very brief period of time. And the

appearance of another soon to be critical mass of human beings, mostly still young, who have already tasted of the better living made possible by these industrial achievements foreshadows an important new cultural emphasis on the well-being of people. In a sense it is almost as if Western civilization had somehow clambered to some new and vast plateau where living will henceforth be easier and the kind of backbreaking effort it took to make the technologic climb is needed no more. Those in the advance see vast new opportunities unfolding before them and they are impatient. They do not see why there cannot be instant well-being for all humans and they question the values of a cultural system which does not appear to them to give this new goal the very top priority.

The new goals and the new emphasis focus on people, on better living, on health and well-being. There is now a search for new cultural values and purposes which will be appropriate or relevant to the new conditions as they are perceived by growing numbers of people. At the moment there is great emphasis on a simplistic egalitarianism which was firmly planted in Western culture at the time of the American and French revolutions. This has already made important contributions but as any student of human nature might suspect, it can never be a fully adequate answer. This is partly because it falsely assumes that everyone has or should have similar or even identical attitudes and views about most things—which is most unlikely ever to be the case—and partly because uniqueness rather than equality is the biological fact. Nor is the current emphasis on existential being, feeling or experiencing, with or without its hedonistic overtones, apt to be very durable as a way of life. Considering the nature of man, and his achievements, it seems most unlikely that this will ever really satisfy healthy members of such a restless, aggressive, achieving species particularly when there is so much yet to be explored and so much yet to be done.

If then the moral and ethical values of the past are now proving somehow less than adequate, and if those in present vogue seem likely to miss the mark, where are valid new values likely to be found? It is suggested that they will evolve from a conception of society which will strive vigorously for a new level of well-being for people, which will acknowledge an almost total dependence on science and technology to accomplish this, and will recognize the bald fact that humans with all their

aspirations for better living and improved technology are for practical purposes encased for all time in an essentially closed biosphere where human nature, human behavior and human society of necessity will become increasingly biologically oriented. The human values which must evolve will more and more reflect this biological orientation.

The case seems easily documented. Many of today's most important unsolved cultural problems can be expressed in terms familiar to the biologist. Since they are also human problems the terms are also familiar to the physician, whose scholarship and practice are rooted in the disciplines of human biology. The problems to be solved pertain to such things as adequate nutrition; unpolluted food, water and air for human consumption; effective reuse or disposal of solid, liquid or gaseous wastes; sexuality and reproduction; genetic health; maturation; tension and unrest; normal and disordered human behavior; aggression, adjustment, satisfaction; learning and transmission of experience among individuals, between cultures, and from one generation to the next; and finally aging and senescence whether these be of individuals, institutions or of whole cultures. The new emphasis on health further substantiates the case. The evidence of a major cultural concern with health abounds. One need only be reminded that the health care industry is now receiving enormous public and private support and will soon be the largest industry in the nation.

There can be little doubt of a great new commitment to the health and well-being of people. The very human character of the many unsolved problems of our culture and the reality of an essentially closed biosphere inexorably set the stage. New cultural values will be needed and many of them

will of necessity be rooted in the best that is known of human biology and medicine. The conclusion seems inescapable that physicians will be involved in establishing many of these new values and that the medical profession will become somewhat of an arbiter of many of the values which will henceforth govern the cultural behavior of humans. The great vision of a new standard of health and well-being for all the human race on Earth, now becoming theoretically attainable by virtue of the successes of the industrial revolution, is a great new challenge to the medical profession in a society which is so clearly subject to biologic law.

Another Wilbur to Chicago

RICHARD S. WILBUR has resigned his chairmanship of the Council to accept a high position with the American Medical Association in Chicago. In so doing he leaves one of the most important posts in American medicine for another. His leadership and organizational skills will be much missed but no doubt the challenges at the national level will make fuller use of his considerable talents. In today's world the medical profession needs leaders who look to the future as well as the past and Dick Wilbur is one of the best of these. Like his uncle, Dwight L. Wilbur, who is now immediate past president of the AMA, he has been tested in the crucible of California medicine and is fully qualified for leadership on the national scene. Not only medicine, but the American public is sure to benefit.

LETTERS *to the Editor*

Aspirin and Salicylic Acid, et al.

To the Editor: The statement of Babb and Wilbur (Calif. Med. 110:440, May 1969) "In our experience, aspirin is a common and often overlooked cause of gastrointestinal bleeding" can be extended to other types of unexplained bleeding, but their assertion that: "Since we know of no accurate method of predicting 'susceptibility,' we must consider aspirin potentially dangerous to anyone" is incorrect. The diagnostic procedure, the aspirin tolerance test,¹ not only reliably detects subjects that are sensitive to aspirin, but furnishes information that throws light on the action of this drug.

Unfortunately knowledge concerning the salicylates is still in a confused state as clearly shown in an excerpt of Engleman (Calif. Med. 110:422, May 1969) in which it is stated: "The drugs of choice—the drug that is recommended almost universally for rheumatoid arthritis—is the salicylate." Equally puzzling are various statements occurring in the Medical Staff Conference: The Clinical Pharmacology of Salicylates (Smith, L. H. and Melmon, K. L., Rowland, M. and Morrelli, H., Calif. Med. 110:410, May 1969). One of these is "Aspirin is hardly new to clinical medicine with regard either to use as a drug or knowledge of the

pharmacological activity. What is known of this activity had been described almost completely before the Christian era." And "Thus aspirin is one of the oldest compounds, senior to quinine colchicine and digitalis." Obviously the confusion stems from the failure to differentiate aspirin from salicylic acid and its various derivatives.

Aspirin is the trade name for acetylsalicylic acid whereas the term salicylates in a strictly chemical sense are the various salts of salicylic acid. Thus, such a drug as salicylamide is not a salicylate. Contrary to the statements made in this conference, salicylic acid is not commonly found in plants whereas the salicyl radical is widely distributed in various species of plants, notably as the glucoside salicin in which the aglycone is ortho-oxybenzyl alcohol. Methyl salicylate, or oil of wintergreen, is one of the few examples of salicylic acid occurring in plants. Aspirin is a synthetic product first prepared in 1853 but not introduced into medicine until 1899. It does not occur in plants and was neither known nor used by any physician before the turn of the century until Felix Hoffmann employed it in treating his father, who had rheumatoid arthritis.

This critical analysis may appear *a priori* as academic, but actually it is of vital importance because aspirin is the most widely used drug of all time and the amount consumed yearly is phenomenal. Sodium salicylate was recognized as an antipyretic and anti-inflammatory agent, particularly efficacious in the treatment of rheumatic fever, long before aspirin was introduced into therapy. Acetylation of salicylic acid to form aspirin produces a new drug with definitely increased analgesic potency, which has led to the wide replacement of sodium salicylate. Unfortunately acetylation also introduced other properties, particularly the effect on hemostasis which is responsible for the bleeding problem.

Acetylsalicylic acid will increase the Duke bleeding time in many presumably normal subjects and significantly in patients with the Minot-von Willebrand syndrome.¹ Such an effect is not produced by sodium salicylate. Since the bleeding time is a sensitive index of the bleeding tendency, no surgical patient should be given aspirin unless his aspirin tolerance test has been checked.² This applies particularly to minor surgical procedures such as tonsillectomy and tooth extraction. Aspirin is contraindicated in hemophilia. It is quite likely that this drug plays an important part in many of the crippling hemarthroses.

Though aspirin has undesirable qualities, it remains one of the most effective analgesic agents, and for all except a small group of subjects it remains a safe drug and this can be assured by the aspirin tolerance test.

ARMAND J. QUICK, M.D.
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Milwaukee, Wisc. 53233

REFERENCES

1. Quick, A. J.: Salicylates and bleeding: The aspirin tolerance test, *Amer. J. Med. Sci.*, 252:265, Sept. 1966.
2. Quick, A. J.: Hemostasis in surgical procedures, *Surg., Gynec. & Obstet.*, 128:523, Mar. 1969.

To the Editor: In response to the interesting note of Dr. Armand J. Quick, Marquette School of Medicine, Inc., Milwaukee, I think that the following points made in relation to articles recently published in *CALIFORNIA MEDICINE* are reasonable. While it would be pleasant to feel that an aspirin tolerance test could well predict the most reasonable doses of the drug to be used in any given individual and that careful administration of the drug would then result in decreased bleeding tendency, it does appear that (1) the pharmacology of acetylsalicylic acid as stated by Dr. Quick will produce the bleeding abnormalities as part and parcel of its other pharmacologic effects; (2) the practical fact in the day to day management of patients is that the tolerance test is not commonly used. This does not excuse the medical community for ignoring a test of usefulness, but it must be borne in mind that acetylsalicylic acid is a proprietary drug in many instances not entirely

under the control of physicians. The relative indiscriminate distribution of the drug, i.e. the amount which is consumed as over-the-counter preparations is going to remain uncontrolled as long as the FDA allows free use of a potentially dangerous compound. In addition, recent data seems to indicate that to some degree this bleeding seems inevitable.

Both the articles by Engelman, et al and Melmon, et al used terminology which was imprecise, but consistent with common clinical phraseology of the drug. The physicians' expression of desirability of aspirin and the universal and preferential use of aspirin for the treatment of rheumatoid arthritis can not be contested. When one considers the alternatives to the use of acetylsalicylic acid, aspirin becomes most certainly the one drug with the highest benefit:risk ratio. Likewise, the authors apologize for the imprecise use of the term *aspirin* for the broader term *salicylates*. Dr. Quick is correct in his chemical classification. Aspirin is only one of many salicylates. His description of the distribution of the salicyl radical in plants is more correct than our own. However, the pharmacology of those compounds containing the salicyl radical seems related to sodium salicylate which is of course close to acetylsalicylic acid. References quoted in the "clinical pharmacology" article contain the details of the history of the development of the synthesis, pharmacologic understanding and use of aspirin which were in part recorded by Dr. Quick. In the United States, our reading of the literature brings us to the view that acetylsalicylic acid has been clinically selected, not so much because of more pronounced anti-inflammatory or analgesic effect above other salicylates but because others have agreed with Felix Hoffman, who when giving acetylsalicylic acid to his father, found the acetyl derivative of salicylic acid rather than the sodium salts of the acid much less irritating to the gastrointestinal tract.

Finally, Dr. Quick's point is well taken in the possible clinical misuse of aspirin, and it is of interest that he pointed out that such misuse might cause critical complications in some patients with leukemia. We agree that this is a distinct possibility. A careful study documenting the later statement made by Dr. Quick would be most helpful to many clinicians.

KENNETH L. MELMON, M.D.
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Information

Aids to Cardiac Diagnosis From Examination of The Cervical Veins

NOBLE O. FOWLER, M.D.

Material Supplied by the California Heart Association

EXAMINATION OF THE CERVICAL veins can sometimes supply information helpful in cardiac diagnosis.

Method of Inspecting The Jugular Veins

The patient should lie so that the thorax is elevated approximately 30 degrees from horizontal, employing a bed or examining table which breaks at the hips, so that the thorax, abdomen, head and neck are elevated, while the lower extremities remain horizontal. The veins are best seen with artificial light directed tangentially across them in order to produce shadows.

Order of procedure: The external jugular veins and the internal jugular veins should be identified bilaterally. In many patients the external jugular veins are invisible. Important information may be missed if the internal jugular veins are not examined. If pulsations are not visible in the internal jugular veins, with the patient's thorax elevated to 30 degrees, then the thorax should be raised or lowered. The internal jugular veins lie deep to the sternomastoid muscles and are best recognized by their broad, undulating, and triphasic pulsations (Figure 1). The A wave is produced by atrial systole. It is the quick wave which just precedes the carotid pulse. The descending limb of the A wave is followed by a negative wave, the x wave, produced by atrial diastole (Figure 2). The x wave is followed by the second positive wave or c wave (Figure 1). The c wave results from bulging of the tricuspid valve into the right atrium as the right ventricle begins to contract; however, in the neck veins the c wave is considerably augmented by the

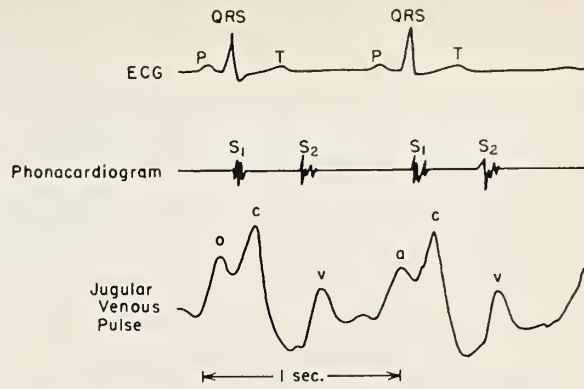


Figure 1.—External recording of normal jugular venous pulse, demonstrating A, c, and v waves. For discussion, see text. From Fowler, N. O., *Cardiac Diagnosis*. Hoeber-Harper, 1968. By permission.

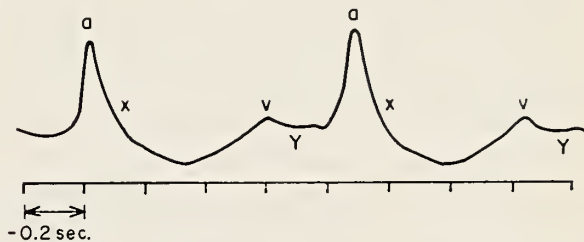


Figure 2.—External recording of jugular venous pulse of a patient with tricuspid stenosis, showing large A wave and slow v descent. From Fowler, N. O., *Cardiac Diagnosis*. Hoeber-Harper, 1968. By permission.

underlying carotid pulse. The third positive wave of the jugular pulse is the v wave, which is produced by passive filling of the right atrium (Figure 1). The descent of the v wave is referred to as the y descent (Figure 2), inscribed as the tricuspid valve opens and blood flows into the right atrium.

When large v waves dominate the internal jugular pulse, as a result of right ventricular failure or tricuspid insufficiency, the venous pulse may be confused with the carotid pulse. The following procedures will distinguish the two. Moderate pressure with a tongue blade or the edge of the hand will obliterate the jugular but not the carotid pulse. If the cervical venous pressure is increased because of right heart failure, abdominal pressure with the hand, sustained for 30 seconds or so, will usually cause the venous pulse to become larger and to ascend higher in the neck (hepato-jugular reflux). With the Valsalva maneuver, the jugular veins usually become more distended but lose their pulsations; not so the carotid arteries. Usually the jugular venous pulses descend lower in the neck during inspiration or when the patient's head is raised, but the carotid pulse is not so affected.

From Cardiac Research Laboratory, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati General Hospital, Cincinnati

*Information Obtained from
Examination of the Jugular Veins*

(1) Estimation of the systemic venous pressure.

When internal or external pulsations are more than 2 or 3 centimeters above the manubrium, one may be confident of elevation of systemic venous pressure, usually from right ventricular failure or constrictive pericarditis. A positive hepato-jugular reflux confirms this observation. The patient must continue to breathe normally and must not perform a Valsalva maneuver during the test. Bilateral non-pulsatile distention of the jugular veins, associated with a collateral venous pattern over the upper chest, suggests superior vena caval obstruction from aortic aneurysm, lymphoma, thymoma, or bronchogenic carcinoma.

(2) Distention of only the left jugular veins.

This usually indicates obstruction of the left innominate vein (kinked left innominate vein). This most commonly results from an elongated aortic arch associated with hypertension or atherosclerosis. However, on occasion, the left innominate vein is compressed by an aneurysm involving the aortic arch.

(3) Prominent A waves in the jugular venous pulse with each cardiac cycle suggest forceful right atrial systole, related either to tricuspid obstruction or increased thickness of the right ventricular wall (decreased compliance). The following clinical causes may be considered:

- (a) *Tricuspid stenosis.* Usually there is accompanying rheumatic mitral disease. The A wave may ascend in the neck during inspiration; normally it descends during inspiration. There are usually shallow and slow x and y descents (Figure 2).
- (b) *Congenital tricuspid atresia.*
- (c) *Right atrial myxoma.*
- (d) *Pulmonary valvular stenosis of moderate or severe degree.* Prominent A waves are ordinarily not to be found in tetralogy of Fallot.
- (e) *Congenital pulmonary atresia with intact ventricular septum.*
- (f) *Pulmonary hypertension.* Mitral stenosis,

lung disease, idiopathic or thromboembolic pulmonary hypertension, or pulmonary arterial branch stenosis may be the cause. Prominent A waves occasionally occur in Eisenmenger's syndrome.

- (g) *First degree A-v block of sufficient degree that atrial systole occurs when the tricuspid valve is closed.* Similarly, large A waves may occur during A-v nodal rhythm.

(4) Irregular giant A waves or cannon A waves.

These may occur with premature atrial or ventricular systoles, if atrial systole coincides with ventricular systole. Irregular cannon A waves also may occur with a regular ventricular rhythm when there is atrioventricular dissociation resulting from complete A-v block, A-v dissociation by interference or paroxysmal ventricular tachycardia. With complete A-v block in adults, the ventricular rate is usually near 40 per minute and there is varying intensity of the first heart sound. With A-v dissociation by interference, the ventricular rate is usually between 60 and 110 per minute. With ventricular tachycardia, the ventricular rate is usually between 130 and 250 per minute. The atrial rate, as judged by the jugular A waves, is most often at the normal sinus rate of 60 to 100 per minute.

(5) *Atrial flutter.* With this one may be able to detect small rapid regular oscillations which occur approximately 300 times per minute.

(6) Prominent c-v waves, with obliteration of the x descent, usually reflect tricuspid insufficiency. This sign is most pronounced in patients with rheumatic mitral disease and rheumatic tricuspid insufficiency; it may also occur with right heart failure.

(7) *The y descent.* Is usually accentuated with constrictive pericarditis (diastolic collapse of Friedreich). Patients with constrictive pericarditis almost invariably display increased venous pressure. Some demonstrate increased jugular distention during inspiration (Kussmaul's sign). This sign may be positive in occasional patients with right ventricular failure, especially in those with restrictive myocardiopathy.



California Medical Association

Kay Elected Chairman Of CMA Council

DR. HAROLD KAY, Oakland, has been elected chairman of the Council of the California Medical Association. He succeeds Dr. Richard S. Wilbur, chairman for two years, who resigned to accept the position of assistant executive vice president

of the American Medical Association, Chicago. Elected to succeed Dr. Kay as vice-chairman of the Council was Dr. John T. Saidy, San Mateo.

Dr. Kay has been vice-chairman of the Council since 1967 and chairman of the Finance Committee. He is a past president of the Alameda-Contra Costa Medical Association.

Dr. Saidy, who was elected to the Council in 1968, is a past president of the San Mateo County Medical Society.

Council Highlights

Highlights of the Actions of the California Medical Association Council Meetings, June 27 to 28, Los Angeles, and August 8 to 9, San Francisco

This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA office.

554th Meeting, June 27 to 28, 1969 Los Angeles

The date of 1 April 1970 was approved for implementation of the 1969 Revised RVS (Fifth Edition). A recommendation also was passed to distribute the new edition—for informational purposes only—to all physicians as soon as possible (to county society officers before the weekend of September 27-28 when the Conference of Component Society Officers is held in Los Angeles).

The role of arbitrator for CMA's Committee on Blood Banks in jurisdictional disputes between blood banks was approved.

A resolution urging county medical societies to co-sponsor at least one cancer conference annual-

ALBERT G. MILLER, M.D.	President
RALPH W. BURNETT, M.D., Bakersfield	President-Elect
WILLIAM F. QUINN, M.D.	Speaker
JOSEPH F. BOYLE, M.D.	Vice-Speaker
HAROLD KAY, M.D.	Chairman of the Council
JOHN T. SAIDY, M.D.	Vice-Chairman of the Council
HELEN B. WEYRAUCH, M.D.	Secretary
MALCOLM S. M. WATTS, M.D.	Editor
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ly, in cooperation with county cancer societies, was approved.

A second symposium on Medicine's Role in Aviation Safety was approved.

A symposium on Emergency Health Services at the 1970 CMA Annual Session was approved.

Appointment of an advisory committee to work with the California Teachers Association was approved. The advisory committee will study the possibility of a health foundation for CTA members and their families.

The Dental Health Council of California was urged in an approved resolution to launch a statewide program for the introduction of fluorides in the state's water supplies. The resolution also calls for CMA cooperation "in such efforts to be kept in proper perspective with medical problems in which the medical profession is interested."

Community Health Week, October 19-25, was endorsed and all component medical societies were urged to participate in activities celebrating this week.

Guidelines for improving relationships with Congressmen and key members of the Administration in Washington, D.C., were approved. The guidelines were developed as a result of a visit to Washington by physicians and staff representing CMA, California Blue Shield and CALPAC.

The Committee on Alcoholism was authorized to work with the California Hospital Association in developing guides for hospitals and their medical staffs. Council approved this action following a request from the CMA Commission on Community Health Services that the Committee on Alcoholism reestablish direct liaison with the California Hospital Association. The main reason is in regard to preparation of policy and guidelines for setting up alcoholic evaluation centers which may be required by future legislation.

The CMA Legislative Committee was requested to develop and support legislation to control and regulate the fitting and sale of hearing aid devices.

An emergency room classification system for hospitals was approved.

A commendation was approved for Department of Health Care Services Director Carel Mulder for his effort to correct misconceptions regarding payments to physicians under Medicare and Medi-Cal.

555th Meeting, August 8 to 9, 1969 San Francisco

A report on medicine's role in new and emerging forms of medical care was approved. Seven recommendations deal with prepaid group practice, neighborhood health centers, multiphasic screening and the health team. The proposals encourage involvement in innovative and experimental programs by component medical societies, co-

operation of voluntary health insurance organizations and a "guidance and counsel" role by CMA and its component societies. The report was submitted to Council by the CMA ad hoc Committee on Health Care. Council voted a commendation to Committee Chairman Arthur F. Howard, M.D., Fresno, and his entire committee for a job well done. Members of the committee are Doctors Homer C. Pheasant, Los Angeles; Albert G. Miller, San Mateo; Herman Stone, Riverside; Robert M. Bartell, San Diego; Ralph W. Burnett, Bakersfield; Milo A. Youel, San Diego, and Jean F. Crum, Downey.

Broad recommendations on rubella vaccination gained approval. Recommendations for vaccination of non-pregnant women of childbearing age and children from one to twelve years of age were prepared jointly by CMA and the State Department of Public Health. Earlier recommendations with children only as the target for vaccination were issued by the U.S. Public Health Service Advisory Committee on Immunization Practices and the American Academy of Pediatrics. CMA and SDPH suggest that component medical societies and local health departments develop community programs to eliminate rubella as rapidly as possible.

Los Angeles County Medical Association was praised in a resolution for telling the public about protective measures to take during severe smog conditions.

California Medicine's annual subscription rate of eight dollars was reduced to four dollars for medical students. This is part of CMA's "Bridge the Generation Gap" program aimed at reaching more medical students.

A public health recommendation calling for government agencies concerned with the control of rat infestation to offer a bounty on rats to the inhabitants of infested areas was approved. This would be a "self-help" program for residents of these particular areas.

The State Water Resources Board was urged to safeguard the state's ocean and waterways against pollution.

A resolution of the San Francisco Medical Society urging preservation and protection of San Francisco Bay against pollution and fill was approved. In order to increase the area of protection the resolution was amended to add the phrase "and its tributaries" following "San Francisco Bay."

556th Meeting, August 9, 1969

Harold Kay, M.D., Oakland, was elected Chairman of CMA Council, following the resignation of Richard S. Wilbur, M.D., Palo Alto. Doctor Wilbur will assume his new position as Assistant Executive Vice-President of the American Medical Association on 1 October in Chicago. John T. Saidy, M.D., San Mateo, was elected Council Vice-Chairman, succeeding Doctor Kay.

1970 ANNUAL SCIENTIFIC ASSEMBLY

of the California Medical Association

San Francisco, March 7-11

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Manpower — new aids to the physician

Systems of delivery for health care services

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If you have a motion picture or exhibit . . . write to the California Medical Association Committee on Scientific Assemblies, 693 Sutter Street, San Francisco 94102, for application forms.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

BENADOM, SAMUEL COY, Lake Isabela (Kern County). Died 21 July 1969 in Canebreak (Kern County) of injuries received in an automobile crash, aged 59. Graduate of State University of Iowa College of Medicine, Iowa City, 1937. Licensed in California in 1938. Doctor Benadom was a member of the Los Angeles County Medical Association.



BIERNOFF, JOSEPH, San Francisco. Died 25 July 1969 in San Francisco, aged 62. Graduate of University of California Medical School, Berkeley-San Francisco, 1935. Licensed in California in 1935. Doctor Biernoff was a member of the San Francisco Medical Society.



BLOOM, A. RALPH, Los Angeles. Died 19 July 1969 in Los Angeles of coronary artery disease, aged 52. Graduate of Boston University School of Medicine, Boston, 1942. Licensed in California in 1948. Doctor Bloom was a member of the Los Angeles County Medical Association.



BROWN, CHARLOTTE M., Los Angeles. Died 10 July 1969 in Los Angeles of pneumonia, aged 90. Graduate of the University of California, Los Angeles Department, 1910. Licensed in California in 1910. Doctor Brown was a member of the Los Angeles County Medical Association.



BURTON, JAMES WILLIAM, San Francisco. Died 18 July 1969 in San Francisco, aged 51. Graduate of Marquette University School of Medicine, Milwaukee, Wis., 1943. Licensed in California in 1943. Doctor Burton was a member of the San Francisco Medical Society.



COZEN, JOHN EDWARD, Los Angeles. Died 25 June 1969 in Los Angeles of cerebral thrombosis, aged 59. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1939. Licensed in California in 1939. M.D. degree from California College of Medicine, 1962. Doctor Cozen was a member of the Los Angeles County Medical Association.



DAHL, CLARENCE A., San Pedro. Died 26 June 1969, aged 67. Graduate of Cooper Medical College, San Fran-

cisco, 1928. Licensed in California in 1928. Doctor Dahl was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



DESMET, DELBERT HENRY, Di Giorgio. Died 14 May 1969 in Bakersfield of hypertensive heart disease, aged 59. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1934. Licensed in California in 1934. Doctor DeSmet was a member of the Kern County Medical Society.



DEWEY, EARLE T., Colfax. Died 29 July 1969 in Weimar, aged 67. Graduate of University of Minnesota Medical School, Minneapolis 1928. Licensed in California in 1931. Doctor Dewey was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.



GAGE, ALAN EDWARD, Los Angeles. Died 27 July 1969 in Glendale of coronary artery disease, aged 82. Graduate of University of Illinois College of Medicine, Chicago, 1912. Licensed in California in 1926. Doctor Gage was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



HARTER, JOHN M., San Francisco. Died 3 July 1969 in Burlingame of cancer, aged 46. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1947. Licensed in California in 1947. Doctor Harter was a member of the San Francisco Medical Society.



HAWKINS, DICKERSON A., Los Angeles. Died 20 July 1969 in Los Angeles, aged 66. Graduate of Meharry Medical College, Nashville, 1932. Licensed in California in 1934. Doctor Hawkins was a member of the Los Angeles County Medical Association.



SCOLES, JACK RAMLER, Irvine. Died 19 July 1969 in Glendale of coronary occlusion, aged 49. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1947. Licensed in California in 1947. M.D. degree from California College of Medicine, 1962. Doctor Scoles was an associate member of the Los Angeles County Medical Association.



SHAW, VAUGHAN ALLISON, Veterans Home (Napa Co.). Died 8 July 1969 in Daytona Beach, Fla., aged 59. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1937. Licensed in California in 1950. Doctor Shaw was a member of the Napa County Medical Society.

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H. Director, State Department of Public Health

Chloramphenicol— Another Warning

CHLORAMPHENICOL has been a popular broad-spectrum antibiotic since its introduction in 1948, because of its effectiveness and the absence of annoying side effects. Since 1952, however, prominent warnings about serious and often fatal blood dyscrasias have been part of the approved labeling of the drug and this information has been widely disseminated in the medical and lay press.

A 1964 study showed that out of a random sample of 138 deaths in California attributed to aplastic anemia between 1 January 1957 and 30 June 1961, a total of 30 patients (22 percent) had had therapy with chloramphenicol.¹

In 1963 two California State Senate resolutions expressed concern about hazards associated with chloramphenicol therapy and asked the California State Department of Public Health and the California Medical Association to investigate further the risk associated with administration of chloramphenicol.^{2,3}

In response to that request, a study was planned and conducted jointly by the Committee on Adverse Drug Reactions of the California Medical Association and the staff of the California State Department of Public Health, with the cooperation of the California Pharmaceutical Association. It was reported to the legislature 1 January 1967 and published in the *Journal of the American Medical Association*.⁴

The study involved a search of death certificates to discover every fatality in California due to aplastic anemia during an 18-month period between 1 January 1963 and 30 June 1964. Out of a total of 409 death certificates referring to hematologic disorders of possible significance, 290 were scrutinized. The cases were assigned to physician-consultants having experience in hematology who reviewed all available material to determine whether or not the diagnosis of aplastic anemia could be made, regardless of cause of death on the death certificate, and whether chloramphenicol or any other identifiable agent was involved.

Among the 290 deaths reviewed, 60 cases of aplastic anemia were found. In ten cases, chloramphenicol had been administered at some time before the onset of anemia. Fatal aplastic anemia developed after a single course of chloramphenicol in five patients, on second exposure several years after the first course in three, and on third exposure in two. Dosage was not unusually large or prolonged in any of the ten patients. Among the 50 patients not exposed to chloramphenicol seven had been exposed to other potentially toxic agents.

The risk of fatal aplastic anemia in association with chloramphenicol was calculated as 13 times that without exposure to the drug. The study team concluded that to assume a probable risk 13 times the normal risk appears totally unwarranted in the treatment of minor conditions or for prophylactic therapy or for treating infections, if a safer alternate drug is available. No reliable way exists to predict in which patients aplastic anemia may develop after chloramphenicol therapy.

A 1969 California State Assembly Resolution relative to the dangers of antibiotic drugs asks that the State Department of Public Health continue its investigation of fatal aplastic anemia and of deaths thought to be due to the use of chloramphenicol, and to send to the Assembly early in 1972 a report of its findings and its recommendations as to needed legislation.⁵

The joint study by the Committee on Adverse Drug Reactions of the California Medical Association and staff of the California State Department of Public Health refined previously available quantitative data concerning the occurrence of fatal aplastic anemia in the California population, and the risk of serious adverse reactions associated with the use of chloramphenicol.

The study also pointed up the value and the need for further cooperative effort by responsible agencies to establish more effective procedures for the evaluation of quantitative factors relating to the occurrence of adverse drug reactions. As pointed out by Weston,⁶ the usual side effects of drugs are reasonably adequately handled from a *qualitative* viewpoint in responsible sources of drug information. However, *quantitative* information, with accurate numerators and denominators or

accurate comparative incidence ratios, leaves much to be desired. Broad programs for the collection of data on adverse drug reactions in recent years have for the most part not provided significant numerator or denominator data bearing on the ratio of risk to benefit. Nor have they delineated the comparative risk-to-benefit ratios of drugs used for similar disease entities. To provide information of this type, more extensive and intensive methods of screening cases and collecting drug usage data need to be developed.

REFERENCES

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2. Senate Resolution No. 150: Relative to the danger of antibiotic drugs, *California Senate J.*, 2:2519, 13 May 1963.
3. Senate Resolution No. 151: Relative to chloramphenicol, *California Senate J.*, 2:2519, 13 May 1963.
4. Wallerstein, Ralph O., Condit, Philip K., Kasper, Carol K., Brown, John W., and Morrison, Florence R.: Statewide study of chloramphenicol therapy and fatal aplastic anemia, *JAMA*, 208:2045-2050, 16 June 1969.
5. Assembly Resolution No. 191: Relating to the dangers of antibiotic drugs, *Assembly Journal*, 2188, 21 April 1969.
6. Weston, Jean K.: Present status of adverse drug reaction reporting, *JAMA*, 203:89-91, 1 Jan. 1968.

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EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA:	California Medical Association For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
LLU:	Loma Linda University For information contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
PMC:	Pacific Medical Center For information contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
STAN:	Stanford University For information contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5940.
UCD:	University of California, Davis For information contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0333.
UCI:	University of California — California College of Medicine, Irvine For information contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
UCLA:	University of California, Los Angeles For information contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
UCSD:	University of California, San Diego For information contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
UCSF:	University of California, San Francisco For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
USC:	University of Southern California For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

CANCER

October 4 — American Cancer Society, California Branch—Annual Scientific Program, "Principles and Problems of Palliation for Cancer" at Hilton Inn, San Diego, Saturday. Contact: Forrest Willett, M.D., Medical Director, ACS, Calif. Div., 875 O'Farrell, San Francisco 94109. (415) 885-5822.

October 17-18—Preoperative and Postoperative Radiation Therapy in the Treatment of Cancer—Fifth Annual San Francisco Cancer Symposium. Zellerbach Saroni Tumor Institute and Dept. of Surgery, Mount Zion Hospital and Medical Center at St. Francis Hotel, San Francisco. Friday-Saturday. Contact: Mrs. Barbara Reynolds, Symposium Sec., Mt. Zion Hospital, 1600 Divisadero, San Francisco 94115. (415) 922-3823. \$40.

November 15-16—Fifth Annual Clinical Cancer Conference. UCSF. Saturday-Sunday.

December 7 — California Tumor Tissue Registry — Semi-Annual Cancer Conference. Beverly Hilton Hotel, Beverly Hills. Sunday. Contact: W. K. Bullock, M.D., Exec. Dir., Los Angeles County Hospital, 1200 N. State St., Los Angeles 90033.

December 13 — Radiotherapy Symposium — Lymphomas & Hodgkin's Disease. Southern California Permanente Medical Group at Ambassador Hotel, Los Angeles. Saturday, 8:30 a.m.-3:30 p.m. Contact: Shirley Gach, Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

MEDICINE

October 1-2—38th Annual Fall Symposium and Second Annual George C. Griffith Lectureship Dinner. Los Angeles County Heart Association at Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: LACHA, 2405 W. Eighth St., Los Angeles 90057. (213) 385-4231.

October 1-3 — Annual Postgraduate Symposium on Heart Disease. St. Francis Hotel, San Francisco. Wednesday-Friday. Contact: Gene C. Taylor, Executive Director, San Francisco Heart Assoc., 259 Geary Street, San Francisco 94102. (415) 982-5753.

October 1-3—Respiratory Disease: Physiological Basis of Diagnosis and Treatment — 6th Annual Postgraduate Course on the Evaluation of Pulmonary Function. TB and Respiratory Disease Association of California at UCLA. Wednesday-Friday. Contact: TB and Respiratory Disease Assoc. of California, 424 Pendleton Way, Oakland 94621. (415) 636-1756.

October 4—Shoek. Woodland Clinic Medical Group, Woodland. Saturday, 9-4:30. Contact: R. C. Edmondson, M.D., Chairman, Professional Day, Woodland Clinic Medical Group, 1207 Fairchild Court, Woodland 95695. (916) 662-4641.

October 4—Inhalation Therapy: Theory and Applications. American Thoracic Society, California Thoracic Society and TB and Respiratory Disease Association of California at UCLA. Saturday. Contact: TB and Respiratory Disease Assoc. of California, 424 Pendleton Way, Oakland 94621. (415) 636-1756.

October 6-17—Coronary Care Unit Program for Physicians. CRMP, Area V at Los Angeles County-USC Medical Center. Two weeks. Course repeated monthly through May, 1970. Contact: Gladys Ancrum, Dr.

P.H., Administrative Associate, CRMP, Area V, 1 West Bay State St., Alhambra 91801.

October 7 — **Evening Lectures in Medicine.** UCSF at Oakland Hospital. Tuesday evenings through Dec. 2.

October 10—**Lesions of the Mouth.** PMC. Friday.

October 18—**Workshop in Arrhythmias (Basic).** PMC. Saturday.

October 23—**Hypertension.** USC at Hilton Hotel, Los Angeles. Thursday.

October 23-26—**California Society of Internal Medicine—Scientific Program.** Coronado. Friday-Sunday. Contact: Cynthia Bell, Exec. Sec., 350 Post Street, San Francisco 94108. (415) 362-1548.

October 29-30—**Symposium of Diabetes.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday.

October 31 — **Endocrinology — 14th Annual Medical Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals. Friday. Contact: Shirley Gach, Symposium Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

November 1-2 — **Coronary Care Symposium.** Orange County Heart Association at Disneyland Hotel, Anaheim. Saturday-Sunday. Contact: Miss Liggett McLaws, Program Director, OCHA, 1043 Civic Center Drive West, Orange 92702. (714) 547-5976.

November 3-14 — **Coronary Care Unit Program for Physicians.** See Oct. 6-17 above.

November 5-6—**Spatial Analysis of EKG.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday.

November 5-6 — **Albert M. Snell Memorial Lectures.** Palo Alto Medical Research Foundation at Palo Alto High School Auditorium. Wednesday-Thursday. Contact: Marcus A. Krupp, Director of Research, Palo Alto Medical Research Foundation, 860 Bryant St., Palo Alto. (415) 326-8120.

November 8-9—**Manipulative Medicine.** USC. Saturday-Sunday. \$50.

November 13—**Office Dermatology.** USC. Wednesday.

November 13-15—**West Coast Allergy Society.** Hilton Inn, San Diego. Thursday-Saturday. Contact: Betty J. Jones, Exec. Sec., P.O. Box 42067, Portland, Ore. 97242.

December 1-12 — **Coronary Care Unit Program for Physicians.** See Oct. 6-17 above.

December 2-5—**Reticuloendothelial Society—6th Annual Meeting.** Jack Tar Hotel, San Francisco. Tuesday-Friday. Contact: Ernest L. Dobson, Ph.D., General Chairman, Donner Laboratory, University of California, Berkeley 94720.

December 4-6—**Cardiovascular Therapeutics.** American Heart Association in cooperation with UCSD at UCSD. Thursday-Saturday. Contact: Eugene Braunwald, M.D., Professor and Chairman, Dept. of Medicine, UCSD.

January 13-14—**The American College of Cardiology—Annual Conference on Cardiovascular Therapy—Medical and Surgical Aspects.** Sacramento. Tuesday-Wednesday. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

Grand Rounds—Medicine

Tuesdays

9-10:30 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Wednesdays

Grand Rounds in Internal Medicine. 10:30-12:00 noon. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

Grand Rounds in Internal Medicine. 12:30-1:30 p.m., University Hospital, UCSD.

Grand Rounds in Internal Medicine. 1:30-3:00 p.m., Fresno General Hospital.

Thursdays

10:30-12:00 noon, Room C3-105, UCLA Medical Center. UCLA.

Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

2-3:00 p.m., Classroom, Third Floor, Fresno General Hospital, Fresno. CRMP Area IV.

Rheumatology Grand Rounds. 11:30 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

OBSTETRICS AND GYNECOLOGY

November 12-16—**Pacific Coast Fertility Society—17th Annual Meeting.** El Mirador Hilton Hotel, Palm Springs. Wednesday-Sunday. Contact: Gregory Smith, M.D., Exec. Sec., Pacific Coast Fertility Society, 909 Hyde St., San Francisco 94109.

December 5-6—**Obstetrics & Gynecology.** PMC. Friday-Saturday.

PEDIATRICS

October 4-5—**Pediatric Neurology.** UCLA. Saturday-Sunday.

October 6-10—**Pediatric Allergy.** UCSF. Monday-Friday.

October 10-11 — **Pulmonary Disease In Childhood.** UCI and CRMP, Area VIII in cooperation with the National Cystic Fibrosis Research Foundation at Childrens Hospital of Orange County, Orange. Thursday-Friday. Contact: William F. Taylor, M.D., Pediatric Pulmonary Demonstration Center, UCI.

October 15—**Newborn Infant Care.** USC. Wednesday.

November 8-9—**Pediatric Neuroradiology.** UCLA. Saturday-Sunday.

November 10-12—**The Fetus and the Newborn.** American Academy of Pediatrics at UCSF. Monday-Wednesday. Contact: William H. Tooley, M.D., 327 Crestmont Dr., San Francisco 94131. (415) 566-7637.

December 6-7—**Second Annual Children's Hospital Medical Center Symposium.** Memorial Hospital of Long Beach, Long Beach. Saturday-Sunday. Contact: Norman R. Nager, Director of Public Relations, Memorial Hospital of Long Beach, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

Grand Rounds—Pediatrics

Tuesdays

8:30 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Conference Room, Sixth Floor, Harbor General Hospital, Torrance. CRMP Area IV.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and the Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Stanford University Medical Center, Palo Alto.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

PSYCHIATRY

October 18-19 — **Adscititious Therapies in Psychiatry.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday.

October 20-24—**Group Therapy.** UCSF at V.A. Hospital, San Francisco. Monday-Friday.

October 24-26—**Southern California Psychiatric Society—Annual Convention.** Biltmore Hotel, Santa Barbara. Friday-Sunday. Contact: Mark F. Orfirer, M.D., 2200 Santa Monica Blvd., Santa Monica 90404.

October 28-Nov. 2—**American Society of Clinical Hypnosis—12th Annual Scientific Meeting and Workshop.** Jack Tar Hotel, San Francisco. Tuesday-Sunday. Contact: F. D. Nowlin, Exec. Sec., 800 Washington Ave., S.E., Minneapolis 55414.

November 1-2—**The Problem of Alcoholism.** UCSF Saturday-Sunday.

November 8—**The Context of Marriage.** UCSF. Saturday.

November 8-9 and 15-16 — **Intermediate Methods in Family Therapy.** UCSF at San Joaquin County Mental Health Services, Stockton. Two weekends.

November 11-16—**Society for Clinical and Experimental Hypnosis—21st Annual Meeting.** Stanford University, Palo Alto. Tuesday-Sunday. Contact: Mrs. Mario Kenn, Society for Clinical and Experimental Hypnosis, 353 W. 57th St., New York 10019.

November 15-16—**Modern Theories in Psychiatry.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

December 6-7—**Therapy in Groups.** UCSF at Mendocino. Saturday-Sunday.

December 13-14—**Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton. Saturday-Sunday.

January 7—**Group Methods.** UCSF at V.A. Hospital, San Francisco. Wednesdays through March 11.

SURGERY—includes Anesthesiology

October 3-4—**Vascular Surgery.** UCSF. Friday-Saturday.

October 6-10—**American College of Surgeons—Annual Meeting.** Fairmont Hotel, San Francisco. Monday-Friday. Contact: John Paul North, M.D., 55 E. Erie Street, Chicago 60611.

October 9 — **7th Annual Sterling Bunnell Memorial Lecture on Reconstructive Surgery.** Departments of Surgery and Orthopaedics, UCSF. Tuesday, 8:00 p.m. Contact: Donald R. Pratt, M.D., 516 Sutter St., San Francisco 94102. (415) 392-3225.

October 12-13—**The Transplantation of Human Organs.** The Medical Group—Honolulu, Research Foundation and School of Medicine, University of Hawaii at Honolulu International Center, Honolulu. Sunday-Monday. Contact: The Medical Group—Honolulu, Research Foundation, 1133 Punchbowl St., Honolulu 96813. \$15.

October 14-22—**Pan-Pacific Surgical Association—11th Congress.** Hawaiian Hilton, Honolulu. Tuesday-Wednesday. Contact: Mrs. Harriet N. DeVault, Exec. Sec., Rm. 236, Alexander Young Bldg., Honolulu 96813.

October 25-29—**American Society of Anesthesiologists—Annual Session.** Hilton Hotel, San Francisco. Saturday-Wednesday. Contact: John W. Andes, Exec. Sec., 515 Busse Highway, Park Ridge, Ill. 60068.

October 31-Nov. 1—**Surgical Emergencies.** PMC. Friday-Saturday.

December 4-6—**Diagnosis and Management of Uveitis—Annual Proctor Foundation Program.** UCSF. Thursday-Saturday.

December 12-14—**Fluid & Electrolytes.** USC at Palm Springs. Friday-Sunday.

January 12-16—**Otologic Surgery.** Los Angeles Foundation of Otology and USC in cooperation with St. Vincent's Hospital at St. Vincent's Hospital, Los Angeles. Monday-Friday. Contact: Glenn Snyder, Managing Director, Los Angeles Foundation of Otology, 2130 W. Third St., Los Angeles 90057. \$300.

Grand Rounds—Surgery

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium,

Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

9:30 a.m., Neuroradiology, 10:15 Neurology, 11:15 Neurosurgery. Stanford University Medical Center, Palo Alto.

Saturdays

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

OF INTEREST TO ALL PHYSICIANS

October 4—**Scintillation Camera Workshop.** UCSF. Saturday.

October 4—**The Drug Scene—What Can and Should be Done About It?** UCLA. Saturday.

October 4-5—**Changing Attitudes Towards Sex.** UCLA. Saturday-Sunday.

October 9-Nov. 13—**Freedom of Choice—The Woman's World.** UCSF. Thursday evenings.

October 11-12—**Health of the School Child.** UCSF. Saturday-Sunday.

October 11-12—**Kern Postgraduate Conference.** Kern County General Hospital at Civic Auditorium, Bakersfield. Saturday-Sunday. Contact: George A. Paulsen, M.D., Conference Committee Chairman, 2603 G St., Bakersfield 93301. (805) 327-7637.

October 17-18—**Thirteenth Annual Western Industrial Health Conference.** Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Mr. B. H. Bravinder, 2180 Milvia St., Berkeley 94704.

October 17-18—**Western Industrial Medical Association.** Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Mr. B. H. Bravinder, 2180 Milvia St., Berkeley 94704.

October 21—**Snicide—A Pressing Social Challenge for Physicians.** Sacramento County Medical Society and UCD in cooperation with Sacramento Academy of General Practice at El Dorado Hotel, Sacramento. Tuesday, 1-5:00 p.m. Contact: Byron H. Demorest, M.D., Program Co-Chairman, Symposium on Suicide, P.O. Box 244, Carmichael 95608.

October 22—**Pacific Hospital of Long Beach—5th Annual Medical Seminar.** Wednesday. Contact: Fred Seligman, M.D., Chairman, Medical Education, Pacific Hospital of Long Beach, 2776 Pacific Ave., Long Beach 90806. (213) 595-1911. \$10.

October 24-25—**Recreation in Rehabilitation.** UCSF. Friday-Saturday.

October 25-26—**How the Patient Affects the Doctor.** UCSF at Fresno Community Hospital, Fresno. Saturday-Sunday.

November 2-5—**California Academy of General Practice—21st Annual Scientific Assembly.** Century Plaza Hotel, Los Angeles. Sunday-Wednesday.

November 15—**Mayo Alumni Association—45th Annual Meeting.** Century-Plaza Hotel, Los Angeles. Saturday. Contact: Office of the 45th Annual Meeting, 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

November 15-16—**Financial, Tax and Investment Planning.** UCLA. Saturday-Sunday.

November 15-16—**Sex and the Professional Man.** Christian Medical Society at Monte Corona Conference Grounds, Lake Arrowhead. Saturday-Sunday. Contact: Albert Holt, M.D., 4080 Hoking Way, Los Angeles 90027.

December 3—**Postgraduate Assembly—"Virology for the Practicing Physician"—St. Luke's Hospital of Pasadena.** At the Huntington-Sheraton Hotel, Pasadena. Wednesday. Contact: W. K. Bullock, M.D., Chairman, 1969 Postgraduate Assembly, 2632 E. Washington Blvd., Pasadena 91107.

December 5-6—**Nasal Obstruction.** A 2-day Symposium on Advances in Diagnosis and Treatment. Of special interest to allergists and otolaryngologists. Stanford University Medical Center. Contact: Richard L. Goode, M.D., Div. of Otolaryngology, STAN.

January 2-4—**Medicine and Law.** The American College of Physicians and USC Postgraduate Psychiatry Dept. at USC. Friday-Sunday. Contact: Donald H. Nastulin, M.D., Director Postgraduate Psychiatry, USC.

January 6—**Neuromuscular Physiology.** UCSF. Tuesdays through April 28.

January 10-11—**Psychiatry in General Practice.** UCSF at Sutter Memorial Hospital, Sacramento. Saturday-Sunday.

January 15-16—**New and Old Antibiotics.** USC. Thursday-Friday.

RADIO-TELEVISION

Medical Radio Conferences. Live from UCSF. Tuesdays, 12:30-1:30. Heard on:

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King City—KRKC	Tulare—KBOS-FM

Southern California's Medical Television Network. UCLA. Weekly broadcasts, Tuesdays 8:30 a.m. Contact: UCLA Medical Television Network.

September 30—**Exercise and the Heart.** CRMP, Area V.

October 7—**Curable Hypertension and Primary Aldosteronism.** (Part I). Boston Medical Reports.

October 14—**Curable Hypertension and Primary Aldosteronism.** (Part II).

October 21—**Common Occurring Cardiac Arrhythmias: Their Recognition and Management.** CRMP, Area III.

October 28—**Lillehei on Stagnant Shock.** Upjohn Films.

Could your patient with cerebral ischemia do a simpler test now

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If you use up the 20 seconds in a single effort, you probably *won't* succeed. Instead, study this for 5 seconds and try to draw it. Then start afresh. Repeat this brief effort four times—for a total of 20 seconds. About fifty percent of college trained people succeed on the fourth trial.¹ Of course, this test is *not* used in patients recovering from cerebral ischemia. However, as a challenge to healthy abilities, it demonstrates the type of task a battery of simpler psychometric tests may use to help reveal improvement in cerebral ischemia.

In a double blind study,² patients on Cyclospasmol (cyclandelate) showed *progressive and significant improvement in mental acuity* on a battery of appropriate, simpler tests.

Specifically, the Cyclospasmol patients had: sharpened reason, imagination, and verbal expressive ability; enhanced orientation to time and space; keener memory for general events; and better recall for past and present personal events. In two out of six measurements no improvement was noted (specifically, short-term memory and constructional skill). However, the overall difference between controls and Cyclospasmol patients in the full battery of tests was judged significant.

In a preliminary uncontrolled study of 20 patients on Cyclospasmol,³ overall significant differences occurred in four of nine sensitive measurements. These were verbal symbolic measurements reflecting high cortical function. Since this was an open study, the authors believe further research with placebo control is needed to validate these suggestive results.

When you choose a vasodilator for cerebral ischemia, consider these benefits:

- Direct action on the vascular musculature of cerebral arterial walls
- Produces a smooth, gradually increasing therapeutic effect which may often become more evident after prolonged therapy
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Look for improvement in cerebral ischemia with **CYCLOSPASMOL**[®] (cyclandelate)

ACTIONS: Cyclospasmol is an orally effective peripheral spasmolytic and vasodilator that acts directly on the vascular smooth musculature to produce a gradual and progressive relaxation that enhances the peripheral and cerebral blood flow.

INDICATIONS: For adjunctive therapy in occlusive and vasospastic diseases of the vascular system associated with an impaired circulation, such as: intermittent claudication; arteriosclerosis obliterans; thrombophlebitis (to control associated vasospasm and muscular ischemia); nocturnal leg cramps; local frostbite; Raynaud's phenomenon; as an aid to encourage healing of diabetic and trophic ulcers of the legs; and for selected cases of ischemic cerebral vascular disease. A faster response may be expected in conditions in which vasospasm is predominant in the pathological process. The drug is not intended to substitute for an adequate medical or surgical program in the treatment of peripheral or cerebral vascular disease. It is imperative that the patient continue to follow established therapy, e.g., foot care, discontinuance of smoking, etc., while taking Cyclospasmol.

Since cerebrovascular disease is diagnosed most frequently only after destruction of nervous tissue, it cannot be expected that signs and symptoms arising from an interruption of neuronal function can be completely reversed by correcting the exciting cause. Nevertheless, restoration of blood flow towards more normal levels with cyclandelate may often produce marked relief from such signs and symptoms as head noises, ringing in the ears, a feeling of weakness, unsteady gait, mental confusion, temporary fluctuations in hearing acuity, poor memory and slurred speech. More important, the drug may provide prophylaxis against further circulatory embarrassment, particularly if the diminished circulation is associated with spasm of the vascular wall.

CONTRAINDICATIONS: Cyclospasmol is contraindicated in cases of known hypersensitivity to the drug.

WARNINGS: Cyclandelate should be used with extreme caution in patients with severe obliterative coronary artery or cerebral vascular disease, since there is a possibility that these diseased areas may be compromised by vasodilatory effects of the drug elsewhere. **USE IN PREGNANCY:** The safety of cyclandelate for use during pregnancy or lactation has not been established; therefore, it should not be used in pregnant women or in women of childbearing age unless, in the judgment of the physician, its use is deemed absolutely essential to the welfare of the patient. Although no prolongation of bleeding time has been demonstrated in humans in therapeutic dosages, it has been demonstrated in animals at very large doses. Therefore, the hazard of a prolonged bleeding time should be carefully considered when administering cyclandelate to a patient with active bleeding or a bleeding tendency.

PRECAUTIONS: Since Cyclospasmol is a vasodilator, it should be used with caution in patients having glaucoma. Consult direction circular before prescribing.

ADVERSE REACTIONS: Gastrointestinal distress (pyrosis, pain, and eructation) may occur with Cyclospasmol. These symptoms occur infrequently and are usually mild. Relief can often be obtained by taking the medication with meals or by the concomitant use of antacids. Mild flush, headache, feeling of weakness or tachycardia may occur, especially during the first weeks of administration.

SUPPLIED: 200 mg. blue capsules in bottles of 100 and 500; 100 mg. orange tablets in bottles of 100 and 500.

May we send you reprints, detailed literature, or professional samples?

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BOOKS RECEIVED

Books received by CALIFORNIA MEDICINE are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.

ACHALASIA OF THE ESOPHAGUS—F. Henry Ellis, Jr., M.D., Ph.D. (Surgery), F.A.C.S., Consultant, Section of Surgery, Mayo Clinic; Professor of Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester; and Arthur M. Olsen, M.D., M.S. (Medicine), F.A.C.P., Consultant, Section of Medicine, Mayo Clinic; Professor of Medicine, Mayo Graduate School of Medicine (University of Minnesota), Rochester. Volume IX in the Series Major Problems in Clinical Surgery, J. Englebert Dunphy, M.D., Consulting Editor. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 221 pages, \$9.00.

ATLAS OF NUCLEAR MEDICINE—Volume 1—Brain—Frank H. DeLand, M.D., Assistant Professor of Radiology, Johns Hopkins Medical Institutions; and Henry N. Wagner, Jr., M.D., Professor of Radiology and Radiological Science, Associate Professor of Medicine, Johns Hopkins Medical Institutions; with the assistance of Wendy A. North, M.I.R., Research Assistant, Johns Hopkins Medical Institutions. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105) 1969. 217 pages, \$18.00.

THE CYTOLOGY OF EFFUSIONS—Pleural, Pericardial and Peritoneal and of Cerebrospinal Fluid—Second Edition—A. I. Spriggs, D.M. (Oxon), F.R.C.P. (Lond), M. C. Path., and M. M. Boddington, M.A., B.Sc. (Oxon), M.C. Path. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 174 pages, \$17.50.

GERMAN-ENGLISH, ENGLISH-GERMAN DICTIONARY FOR PHYSICIANS—2nd unrevised edition in two volumes. Volume II, English-German—Fritz Lejeune and Werner E. Bunjes. Intercontinental Medical Book Corporation (in the U.S.A., Canada, and South America), 381 Park Avenue South, New York, N.Y. (10016), 1969. 738 pages, \$18.75.

INFLUENCING SMOKING BEHAVIOR—A Report of the Committee for Research in Smoking Habits Appointed by The Norwegian Cancer Society (UICC Technical Report Series, Vol. 3)—Edited by J. Wakefield. This book is available from: International Union Against Cancer, P.O. Box 400, 1211 Geneva 2, Switzerland, 1969. 90 pages, \$2.00 (Paperback).

INTERNAL MEDICINE IN WORLD WAR II—VOLUME III, Infectious Diseases and General Medicine (Medical Department, United States Army)—Prepared and published under the direction of Lieutenant General Leonard D. Heaton, the Surgeon General, United States Army. Colonel Robert S. Anderson, MC, USA, Editor in Chief, and W. Paul Havens, Jr., M.D., Editor for Internal Medicine. Office of the Surgeon General, Department of the Army, Washington, D.C., 1968. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C., 20402, \$8.25. 778 pages (Buckram).

PHYSIOLOGY OF THE HUMAN KIDNEY—Laurence G. Wesson, M.D., Professor of Medicine and Head of the Division of Nephrology, The Jefferson Medical College of Philadelphia, Pa. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 712 pages, \$34.00.

A TREATMENT MANUAL FOR PATIENTS WITH PULMONARY EMPHYSEMA—Alvan L. Barach, M.D., Consultant in Medicine, The Presbyterian Hospital, New York, New York. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 101 pages, \$4.95.

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TEACHING PSYCHOTHERAPY OF PSYCHOTIC PATIENTS — Supervision of Beginning Residents in the "Clinical Approach" — Elvin V. Semrad, M.D. Editor: David Van Buskirk, M.D. Workshop Collaborators: Dan H. Buie, Jr., M.D.; John T. Maltzberger, M.D.; Elvin V. Semrad, M.D.; Julius Silberger, Jr., M.D., and David Van Buskirk, M.D. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 122 pages, \$5.75.

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New Concepts in Cancer Control

Preventable and Avoidable Cancers

WENDELL G. SCOTT, M.D., *St. Louis*

THE HONOR OF GIVING the L. Henry Garland Memorial Lecture is one which I have cherished because of my long friendship with this dynamic, effervescent and inspiring man. Harry and I were contemporaries in radiology. It was my privilege not only to nominate him for the presidency of the American College of Radiology, but also to be one of his sponsors for its gold medal.

Rather than eulogize Harry, which has been done so beautifully by his great and good friend, Dr. Dwight Wilbur¹ and by our colleague, Dr. Philip Hodes,² I am going to tell you about some of my personal experiences with this exceptional man. In the later years of his phenomenal career we worked together very closely when our interests became focused on the problems of cancer control. We both became involved in the American Cancer Society, Harry as a member of the National Advisory Committee on Research on the Therapy of Cancer and I as chairman of the national Medical and Scientific Committee.

Harry had an intuitive sense—almost an instinct—for penetrating the heart of a problem and arriving at a decisive opinion. It was either black or white and one which he would vigorously defend against all challenges. Yet, if further debate developed a more constructive or more certain approach, he would accept it. Later, when I became a member of the Editorial Board of *CA* and then

editor of *Cancer*, the mail almost every week contained a brief, concise and spirited note either commending or criticizing a particular article or issue. If in his opinion an article had overemphasized the efficacy of a surgical procedure or failed to give radiation therapy its just position in the management of that malignant disease, he would suggest a counterattack by developing an article on the effectiveness of radiation treatment. I have missed these spicy and sometimes jolting notes, for they always stimulated a responsive action. To him we owe a great debt for his fearless, unflinching and courageous efforts to help establish the place of radiation therapy in the management of cancer. It is most appropriate that the California Radiological Society has dedicated this lectureship to memorialize the indomitable and flaming spirit of L. Henry Garland, a man of incessant energy and devotion to the advancement of radiology. I have chosen for this lecture the title "Preventable and Avoidable Forms of Cancer," because the field of cancer prevention intrigued Harry and because it offers greater possibilities for the control of cancer and the saving of lives than any other measure at our command today.

The magnitude of the problem and the possibilities of achieving success become apparent when we realize that 16 percent of the deaths from all causes in the United States are due to cancer. The age-adjusted death rate from cancer per 100,000 population has increased from 112 in 1940 to 128 in 1965. This year (1969) about 325,000 persons will die of cancer, about 900 each

¹The L. H. Garland Memorial Lecture, presented at the 98th Annual Session of the California Medical Association, March 15 to 19, 1969.

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day. Of every six deaths, one is from cancer. About 940,000 Americans will be treated for cancer, newly diagnosed in 615,000 of them. Of Americans now living more than 50,000,000 will eventually have cancer—one in four of us; and two of every three families will have an experience with it.

On the bright side 1,500,000 Americans are alive today who have been cured of cancer for at least five years—one out of every three have survived. The majority of cancer deaths occur in persons over 65 years of age. In women age 30 to 54 it is the leading cause of death. Since 1949 more males die of cancer than females, largely due to the increase in lung cancer. In 1969 the ratio will be 55 males to 45 females.

The leading sites of cancer causing death in males are: to age 34, the blood; age 35 to 75, the lung; 75 and over, the prostate. In females the ranking is: under age 15, leukemia; age 15 through 34, the uterus; 35 to 74, the breast; age 75 and over, the colon and rectum.

In children cancer deaths are exceeded only by accidents—causing 4,000 deaths under age 15, about half of them from leukemia. Today there are more than 300,000 children under 18 who have lost their fathers from cancer and 250,000 who have lost their mothers.*

These are the stark realities. This is why the prevention of cancer should concern us. As radiologists we see more patients with cancer than any other medical specialty. In diagnostic radiology the large majority of the examinations are concerned with identifying the presence of cancer or in ruling it out. More than 50 percent of all cancer patients will at some time undergo radiation treatments. Radiologists should be among the leaders in initiating cancer detection programs, in supporting measures for controlling carcinogenic pollutants in the atmosphere, in the water and in the earth. They should actively support legislative and public health measures designed to study possible carcinogens in food preservatives and additives, in fungal contaminants and in cosmetics and medicinal preparations. They should support measures for the control of unnecessary radiation exposure as well. There are unlimited opportunities to provide leadership to volunteer cancer and other health agencies, to appropriate committees in organized medicine, to governmental health advisory

councils and to those of the National Institutes of Health in the development of effective programs for cancer control. Above all, we should set the example for our medical colleagues, for our patients and for our friends by refraining from indulging in the use of known carcinogens.

Sir Alexander Haddow³ when president of the Ninth International Cancer Congress in 1966, stated: "It would appear that the majority of human cancers are avoidable"—these are the cancers that are influenced by extrinsic environmental factors, directly or indirectly. They include many tumors of the respiratory system; the gastrointestinal and urinary tracts; the skin and mouth; the hormone dependent organs such as breast, thyroid and uterus, and the blood and lymphatic systems. These are the cancers that I refer to as preventable and avoidable cancers and cancers arising from personal indifference.

The "Class Consciousness" of Cancer

Socio-economic factors also exert a strong influence on the control of this group of cancers. Breslow⁴ in a study of the California Tumor Registry demonstrated what he calls the "class consciousness" of cancer and its treatment, namely that:

1. Cancer of the cervix is twice as frequent in the lowest income group as in the highest.
2. Among men, lung and stomach cancer strikes the lowest income group twice as frequently as it does those with the highest income.
3. Only one-third of the cancer patients in county hospitals had received the benefits of early diagnosis while one-half of those in private hospitals received these benefits.
4. Sixty-two percent of private hospital patients with cancer of the cervix survived five years or more but only 39 percent of the county hospital patients.
5. Alameda County reported two-thirds of the women in the highest social class had received at least one Papanicolaou test while only one-third of those in the lowest economic group had received such a test.

It is unfortunate that the largest portion of the population should benefit the least from cancer control measures. This imbalance must be corrected by new and expanded programs.

The identification of environmental factors that have a causal relationship in the development of cancer and the elimination or protection against

*All cancer statistics taken from "1969 Cancer Facts and Figures," Published by the American Cancer Society, Inc., 219 East 42nd Street, New York, N.Y. 10017.

them can provide a short cut for the control of many cancers. The classical example and the first identification of an environmental chemical causative agent of cancer in man was cancer of the scrotum. It was a common occurrence among chimney sweeps, nearly 100 times more frequent than in the general male population, and was caused by their years of contact with soot. When this was recognized by Sir Percival Pott⁵ in 1775, protective clothing and cleanliness were instituted and this avoidable cancer has practically disappeared.

The most common of all cancers, cancer of the skin, is an avoidable cancer. It is induced by prolonged over-exposure to sunlight, to ultraviolet lamps, to arsenic, to certain oils and chemicals, all of which agents it is possible to avoid, and thus to prevent this form of cancer. Because it occurs on the skin, it is easily seen, recognized early, promptly treated and cured. The cure rate for skin cancer is 93 percent in the United States, but because of the high incidence the 7 percent failures account for over 4,000 unnecessary deaths every year.⁶

Industrial Prevention Programs

Large industries were among the first to recognize the value of cancer prevention programs. For example, Eckardt,⁷ the director of the Medical Research Division of Esso Research and Engineering Company of New Jersey, instituted a cancer detection examination at the time of the employees' periodic health check-up and provided prompt treatment of any malignant or pre-malignant lesions found. The company constantly studies working conditions to eliminate the possible exposure of workers to carcinogens in that industry. So successful has been this program that after 20 years the company has not had a single case of cancer that could be attributed to oils. In the beginning they found that cancer to the scrotum was developing in some of their wax pressmen—in 11 among 77 of them. As these men worked at their tables they pressed the frames containing wax and oils into the crotch of their pants, which became saturated with these materials. This practice was stopped, the men were required to take showers at the end of the day and to wear a clean uniform daily, and there has been no further incidence of this particular cancer.

Another preventable cancer occurred in the bladder of upwards of 70 percent of the chemical workers that were heavily exposed to aniline dye

intermediates, and especially to betanaphthylamine.⁸ When this chemical was identified as the culprit and exposure to it was stopped, this particular cancer disappeared and the overall incidence of bladder cancer in this group of men returned to normal. Wynder and associates⁸ showed that cancer of the bladder is predominantly a male disease, that it is increasing in some countries, including the United States, and that cigarette smoking increases the risk of bladder cancer by about two-fold. They also pointed out that shoe repairers appear to have an inordinately high incidence of bladder cancer and that they should be advised to handle dyes and polishes with more care, and to wash their hands frequently with soap and water as a means of reducing their higher risk. Another lead is the recent report by Bouser⁹ that about 50 percent of all patients with bladder cancer have abnormal tryptophan metabolites in their urine—an important observation that is being investigated.

It has long been known that about 50 percent of the miners in the pitchblende mines in Joachimsthal¹⁰ and about 75 percent of the miners in Schneeberg,¹⁰ both in Czechoslovakia, dying from natural causes, died from cancer of the lung brought about by prolonged exposure to radioactive ores. A similar high incidence of lung cancer has appeared among the uranium miners in the Colorado plateau due to their excessive inhalation of radon gas.^{11,12} By periodic cytologic examination of the sputum of these miners, it is possible to detect the presence of abnormal cells that are believed to be the precursors of malignant changes in the bronchial mucosa. When such cells appear in the sputum of a miner he is removed from the mine, given a job above ground, and instructed to stop smoking. Usually the cells in the sputum will slowly return to normal, and presumably he has avoided development of a pulmonary cancer.

Among chromate ore workers the estimated lifetime incidence of lung cancer was approximately 35 percent.¹³ Workmen who inhaled beryllium salts and oxides¹⁴ also had a higher incidence of lung cancer. The inhalation of asbestos fibers¹⁵ is known to be a responsible agency in the causation of lung cancer as well as of malignant mesotheliomas of the pleura and peritoneum. Even the inhalation of a small amount of asbestos fibers¹⁶ seems to be capable of giving rise to these malignant tumors.

In the 1930s fatal bone cancers appeared in women who had ingested minute quantities of

radium over the years by habitually "pointing" their brushes in their mouths as they painted luminous dials on watches and instruments. These were accidentally induced cancers which are now avoided.

It is a curious but well established fact that the incidence of cancer of the ethmoid sinuses is high among men refining nickel ores.¹³ Another substance, cobalt,¹³ when accidentally injected or thrust beneath the skin almost invariably caused a cancer to develop at that site. Fortunately, exposure to all these carcinogenic substances can and is being eliminated by modern protective industrial practices and these cancers avoided.

The most important environmental causal agent in the production of internal cancer today is, of course, the prolonged inhalation of cigarette smoke. The Second Report of the Surgeon General of the United States Public Health Service, "The Health Consequences of Smoking," issued in 1967, reviewed more than 2,000 additional research studies, all done since the 1964 report. They confirmed and strengthened the conclusions of the initial report that the inhalation of cigarette smoke was the major cause of lung cancer, and in addition brought out:

1. That a "substantial" increase occurs in the mortality ratios for smokers, especially cigarette smokers, from cancer of the oral cavity and pharynx.

2. That "cigarette smoking is a significant factor in the causation of cancer of the larynx."

This latter conclusion was strengthened by von Essen and associates¹⁷ who in December 1968 reported on "Cancer of the Larynx in Connecticut." For the period 1935-1959 there were 1,438 cases with a male to female ratio of 12:1. The annual age-adjusted incidence for laryngeal cancer rose from 3.8 to 6.1 per 100,000 males during this 25 year period—a rise paralleling the spiralling incidence of lung cancer.

The smoking problem can be summarized by saying it is tragic that the medical profession and the public have been so long in recognizing that cancer of the lung is largely an avoidable cancer and that cancer of the oral cavity, pharynx and larynx probably belongs in this category. These cancers for the most part are, then, due to the personal indifference of the individual.

As recently as ten years ago or even five years ago, how many physicians would have predicted that today cancer of the cervix would be con-

sidered an avoidable cancer? Twenty years ago this cancer was the No. 1 killer of women. In the last 25 years the death rate from cervical cancer has dropped 50 percent. The widespread application of the "Pap" test, named after the late Dr. George Papanicolaou, has made this possible. By this test cancer can be found in its earliest stages, before it becomes invasive, before it can be seen by the naked eye, and at a time when it is practically 100 percent curable. Yet after 25 years it is estimated that 60 to 70 percent of the adult female population are still unscreened—30 to 40 million women.

The effectiveness of the "Pap" test in the control of cervical cancer has been demonstrated in Louisville, Kentucky,¹⁸ where Pap smears have been done on a large group of women for the past ten years. For the last seven years not one single case of invasive cancer of the cervix has appeared among these women, proving that yearly cytological screening provides essentially 100 percent protection. Today one can say that a death from cancer of the cervix is a preventable death. It need only occur from personal indifference or self-neglect.

It may also be considered an avoidable cancer as well, for cervical cancer has a much higher incidence in countries where adequate personal hygiene is difficult to obtain, such as in the countries of Latin America, India, China and Africa, and has the lowest incidence in countries in which the plumbing facilities are better. In Singapore it was demonstrated that those women who have access to a private bathroom have a lower incidence of cervical cancer than those who do not. It is twice as high in women who marry at 16 years of age or younger and who initiate sexual intercourse at an early age. It occurs more frequently in married than in unmarried women. In women married twice or more, the incidence jumps about three times. Prostitutes have a very high incidence.

In studies of 13,000 nuns in the Province of Quebec, of 100,000 nuns in the United States, and of nuns in several European countries, no cervical cancers were found or no deaths from cervical cancer were reported,¹⁹ indicating that cervical cancer is very rarely found in the absence of sexual intercourse. In contrast, however, Wynder found that nuns had cancers of the body of the uterus, of the ovary and of the breast, and that the incidence of endometrial cancer in them was higher than in the average female population.

A somewhat related and another avoidable cancer of the penis—related because wherever the incidence of cancer of the cervix is low, so is the incidence of penile cancer, and where one is very common, so is the other. Penile cancer is probably the oldest of avoidable cancers. It has been almost non-existent among the Jews in whom circumcision is performed at the end of the first week after birth as part of a religious rite. In Moslems circumcision is carried out before puberty, and they also have a low incidence of this cancer. In a series of 120 cases of this cancer at New York Memorial Hospital for Cancer and Allied Diseases, Dean²⁰ reported that none of the patients had been circumcised in infancy. It has also been established that circumcision after the age of puberty is ineffective. In a country as health conscious as the United States, this cancer could be largely eliminated by circumcision and personal cleanliness. Where these practices are neglected, the incidence is considerably higher, as in Ceylon, South Africa and Latin America. In India it may account for as much as 10 percent of all cancers in males and, in China up to 20 percent. Mexico may have the world's highest known incidence of this disease. In the United States it amounts to from 1 to 3 percent of all cancer²⁰

Cancer Related to Social Customs

The social customs that can lead to cancer are complex, deeply rooted, and apparently satisfy strong human desires. For example, the Cancer Institute of Madras in India²¹ reports that 48 percent of all malignant neoplasms were oral or pharyngeal in origin, with more than 20 percent of them arising from the buccal mucosa. In contrast buccal cancers in the United States account for only 4.6 percent in males and 1.7 percent in females.²¹ The high incidence of intraoral cancers also prevails in the Philippines, Ceylon, Burma, Pakistan, Guam and Russia and is most frequent in the low income groups there. It is probably related to the national habit of chewing a mixture of tobacco and slaked lime with betel nut. This "quid" is placed in the chewer's mouth between the cheek and the gum and kept there most of the day. It stains the teeth and keeps the mouth filthy. These "self-induced" cancers are pitiful to see.

A similar habit exists in the southeastern United States. It is "snuff-dipping," and is fairly common, especially among the older women in the low income groups. Snuff is no longer sniffed into

the nose as was fashionable in the 18th century. Today a pinch of this flavored, powdered tobacco is placed in the gingival buccal gutter. The prolonged contact of the quid with the limited area of mucosa produces a severe chronic local irritation that is an ideal environment for any carcinogen in the mixture to exert its effect by direct contact.²²

Snuff dippers' intraoral cancers are not just a casual or freak occurrence. Brown and associates,²³ of Atlanta, recently reported on 394 cases of oral cancer in which 78 percent occurred in the buccal gutter and were in women. Seventy-five percent of these women were confirmed snuff users and kept the quid at that location. Rosenfeld and Calloway,²⁴ reporting from Nashville, Tennessee, found that 90 percent of the women in a group with 525 intraoral cancers had carcinoma of the gingiva-buccal area and were habitual users of snuff. In contrast are reports from Buffalo, the Mayo Clinic, and New York City, in which cancers of the oral cavity and pharynx occur about five times more frequently in men than in women.^{25,26,27}

Cancer of an unusual type that is suspected of having a causal relationship to environmental factors is Burkitt's sarcoma. It was first thought to be limited to African children, but more thorough studies revealed that it can appear in children of all races—American, European, Asian and Indian, but the strikingly high incidence occurs only in a zone across Central Africa with an elevation of less than 5,000 feet, an annual rainfall of more than 200 inches and a temperature that does not fall below 60 degrees Fahrenheit. These conditions raise the question: Could this type of cancer be due to a virus that was possibly transmitted by a vector such as a mosquito? Dorfman²⁸ suggested that the unusually high incidence in a particular area in Africa, the predilection for the bones of the jaw and face and the rarity of leukemic transformation may reflect an attendant host susceptibility in African children in addition to the environmental factors.

There is another group of cancers which appear to be related to causal factors in our environment, but the factors have not yet been identified. The first of these is cancer of the stomach, which has been undergoing a remarkable decline for the past 30 years in the United States for no known reason. At the same time cancer of the stomach has been increasing in Yugoslavia, Mexico, India, the Soviet

Union, Iceland and, particularly, in Japan, where it is the No. 1 cancer. Yet the Japanese who live in the United States do not have the same high incidence. Why? It might be related in some way to the low protein diet of these people, but this is not certain. The disparity in the incidence among these different peoples apparently lies in differences in their environmental food habits. It is now known that aflatoxin as produced by the fungus *Aspergillus Flavus* growing on spoiled peanuts is, according to Bouser,⁹ among the most potent carcinogens known. It is believed to interfere with the synthesis of DNA. Aflatoxin has also been obtained from the fungus that grows on moldy rice. Since the poorer quality of these foods is more likely to be contaminated by such fungi and since the highest incidence of stomach cancer occurs in the lower income groups, it is easily understood why aflatoxins have become suspect and are under serious investigation.

Epidemiologists would like to know why American women have about seven times more cancer of the breast than Japanese women. They think that there is some connection in the length of time they spend in nursing their children, but much more research is needed into glandular and related functions to make sure. They would also like to know why cancer of the breast is more frequent in unmarried than in married women.

American Indians and Eskimos of both sexes are said to have a low cancer rate generally, for which there is no explanation. The Indian women, however, have a normal or higher mortality rate from cancer of the liver and uterus.

Cancer of the colon and rectum in the United States is the No. 1 internal cancer among men and women; 46,000 deaths will occur from it this year, and there will be 76,000 new cases. It is the only cancer in which the incidence is the same in both sexes. Yet in the same countries that have a high incidence of cancer of the stomach there is low incidence of cancer of the colon. It is infrequent in Mexico, Latin America, India and in Japan.

Haenszel²⁹ of the National Cancer Institute has shown that the incidence of cancer of the colon in people who live in urban communities is higher than in those dwelling in rural communities, and that there is an appreciably higher rate in people of the northern part of the United States than in those of the southern states. These findings remain consistent in migrants from the northern states to

the southern states, and vice-versa, as well as migrants going to and from rural and urban centers.

It is interesting that colon cancer occurs only one-tenth as frequently among the members of the Bantu tribe in Southeast Africa as it does in the United States. Yet cancer of the liver which accounts for 50 percent of all cancer deaths among the Bantus, accounts for less than 4 percent in Europeans and North Americans.³⁰ Again a search must be made to identify environmental factors that account for these contrasting incidences. Scientists speculate that the Bantu tribesmen exist on a diet deficient in milk and meat, particularly in the early years, which predisposes them to cirrhosis of the liver, from which this form of cancer appears to develop. Here then is the opportunity to identify other environmental factors and add to the list of preventable cancers.

In Puerto Rico³⁰ the frequency of cancer of the esophagus is ten times higher than in upper New York State. The physicians in Puerto Rico strongly suspect that it is due to the practice among the lower socio-economic groups of drinking bad rum which they make in their homes.

Mention can only be made of the intricate problems of the carcinogenic potentials of pesticides, of food additives—such as colors, flavors, emulsifiers, antioxidants and fungal contaminants, although many are suspect. Likewise, cosmetics and certain medical preparations can only be mentioned, because they are very complex and much work needs to be done in this field. The Federal Drug Administration has taken an interest in these products and they are now under serious investigation.

The concept of avoidable cancers is not new, it has been utilized by industry for years. But what is new is that more of the factors that can induce cancer are being identified and that a continuing organized and intensified effort is in operation to detect new ones.

The concept of preventable cancers is relatively new, but it did not achieve important recognition until the Pap test was introduced and finally accepted. The recognition that means for the prevention of cancer can be developed, can be practical and can be applied to large populations has been a great achievement in the control of cancer. It cannot be foretold at this time what magnitude of cancers may fall into this group until more knowledge and the results of research are accumulated, but there will be many.

The concept that cancers can arise from personal indifference is new and one which deserves both professional and public acceptance.

With the understanding of these concepts, it becomes apparent that cancer is largely a social problem and that public health measures can be developed that could lead to the control of a majority of the cancers today. Cancer of the cervix has already been conquered. Cancer of the lung is reasonably understood, the major causal factors have been identified, and all that remains to eliminate 80 to 85 percent of lung cancers is to gain an acceptance of existing educational programs and to change the social complex that promotes the desirability of smoking. Cancer of the colon and rectum are slow to metastasize and the survival rate associated with them if treated before spread has occurred is high—70 percent. Annual sigmoidoscopic examinations for populations in western Europe and North America can provide for the detection of this cancer in more than 50 percent of cases at a stage when there is an excellent chance of cure. Fortunately increased interest and efforts are being directed to find the etiological factors involved in colon cancer. The answers may come from further epidemiological studies and geographic pathology. While we are awaiting the final solution of the cancer enigma that will come from further basic research, great efforts are justified for the full development of programs on avoidable and preventable cancers and those arising from personal indifference. For the past two decades the great emphasis has been on furthering cancer research, and rightly so. The time has now come to direct emphasis to the prevention and avoidance of cancer and to teach people that cancers can arise from self-neglect.

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Neurosurgical Aspects of Unexplained Unconsciousness

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■ *Neurosurgical experiences and diagnostic difficulties with unconscious patients without diagnosis included cases of intracranial neoplasia, cerebral arteriosclerosis, subdural hematoma, traumatic subcortical hemorrhage, subdural abscess, rheumatic encephalitis, spontaneous subarachnoid hemorrhage, subacute bacterial endocarditis and emboli, myocardial infarction and emboli, spontaneous subcortical hemorrhage, fat embolism, meningitis, drug intoxication, uremia, cases in which the cause of death was not clearly established, and phycomycosis of the central nervous system.*

THE DIFFICULTIES in diagnosis and treatment of a patient who is unconscious when first seen present an emergency of challenging character. A rapid and systematic approach as well as a broad knowledge of disease is essential, with ready resort to all logical procedures and consultations necessary. In some hospitals where the incidence justifies, "Coma Units" have been organized. Moreover, in well organized emergency departments efficient and rapid diagnostic evaluation and treatment should be anticipated.

In this communication representative experiences are described, some unusual in character.

Intracranial Neoplasms

During her sixth month of pregnancy, a 30-year-old woman developed left-sided convulsions followed by coma. During the previous three years

she had had occasional right frontal headaches, attributed to tension. At first the convulsions were generalized before becoming left-sided.

The following day she was transferred by ambulance from Taft to Santa Barbara, California. When examined there, both optic discs were slightly elevated, and in association with the left-sided convulsions there was a bilaterally positive Babinski reaction. Other than the finding of a pregnancy of five or six months, the general physical examination was not unusual. It seemed likely the patient had a glioma in the right cerebral hemisphere.

Ventriculography confirmed the impression of a tumor in the right frontal area. A large parasagittal meningioma was removed. The postoperative course was gratifying. In a few days she regained consciousness and was discharged on the 19th postoperative day. Three months later she delivered an 8½ pound baby spontaneously. When last heard from almost 20 years later, mother and daughter were doing well.

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Cerebral Arteriosclerosis

A woman of 47 years of age had memory lapses, headaches, and episodes of vertigo followed by confusion. When seen in consultation she had a slight right hemiparesis, was incontinent, confused and aphasic. The rapidity of onset and progression suggested a malignant lesion in the left frontal area. Ventriculography revealed moderately dilated ventricles in their normal position. It was believed this excluded a tumor and suggested some degenerative process. The patient's condition became progressively worse and she died a week after the onset of symptoms.

The salient postmortem findings included advanced cerebral arteriosclerosis with thrombosis of the basilar artery. There was a recent encephalomalacia of the right frontal and occipital lobes. Additionally there was moderate arteriosclerosis of the aorta and coronary arteries, and bronchopneumonia.

Subdural Hematoma

On the evening of 22 December 1959 a 61-year-old executive was seen in emergency when he suddenly became comatose. He had been receiving anticoagulant therapy for cerebral thrombosis. When hematuria developed, the drug was discontinued. On examination, left hemiparesis and dilatation of the right pupil were noted. It was believed he had either a subdural or subcortical hemorrhage on the right side.

At operation a thick subdural hematoma was evacuated and drained. No lesion was found on the left side. The patient recovered promptly and when last seen seven years later was well.

A 48-year-old, confused and hypertensive Negro was hospitalized by ambulance 1 March 1952. Laboratory data were not revealing. While it was believed the confusion was the result of hypertensive encephalopathy, it was considered important to exclude an expanding lesion by pneumography. Ventriculography 13 March revealed a tumor in the right frontoparietal area.

A small, right frontotemporal osteoplastic craniotomy exposed a thick subdural hematoma which was evacuated and drained. The first few postoperative days he was less responsive than anticipated, but then improved and was discharged. He was readmitted the following day in an unconscious state. His daughter-in-law said he appeared

well during the day, but shortly after midnight vomited, became stuporous and then unconscious.

On readmission his blood pressure was elevated, both pupils constricted, the neck rigid, and the Babinski sign positive bilaterally. Lumbar puncture revealed a pressure of 440 mm of bloody fluid. Gradually he improved and by the fourth day was able to take fluid. On the fifth day, however, he became stuporous and died the following morning. It was believed the last episode was the result of a cerebrovascular accident.

Postmortem examination disclosed multiple congenital aneurysms of the right anterior cerebral and communicating arteries rupturing into the cerebral ventricles. The right parietal lobe contained a mass 25 by 35 mms, composed of congeries of thin-walled vascular spaces filled with clotted blood. A section of this vascular tumor showed numerous large vascular channels, both arterial and venous.

On the morning of 17 June 1965, a comatose, married woman of 51 years was seen as an emergency. She had a history of chronic alcoholism. In 1958 she had been in a Los Angeles hospital in hepatic coma for two weeks. In April of 1959 she was discharged from a Santa Barbara hospital with the diagnosis of polycirrhosis. On 5 June 1965, she was admitted in an unconscious state with seizures. There was a history of her falling on June 1st. The diagnosis was that of chronic alcoholism with hepatomegaly. On 17 June a spinal fluid pressure of 240 mms of slightly xanthochromic fluid was recorded.

On examination the liver was found enlarged, the right pupil was dilated, there was weakness of the left arm and leg, early papilloedema, and bilaterally positive Babinski reactions. It was believed she had a subdural hematoma and that immediate operative intervention was necessary. Such was done under local anesthesia with the evacuation of a large subdural hematoma on the right side. None was uncovered on the left side. Pathologically the neomembrane exhibited fibrovascular organization of an estimated three or more weeks.

By 27 July her level of consciousness had improved sufficiently for her transfer to a convalescent hospital. Subsequently her condition gradually deteriorated with death occurring two months later. Unfortunately a postmortem examination was not obtained.

Traumatic Subcortical Hemorrhage

A soldier who had been briefly unconscious from an automobile accident, became drowsy five days later and left hemiparesis developed. The spinal fluid was xanthochromic and the pressure 260 mm of water. There was no skull fracture. A left-sided Jacksonian convulsion, followed by coma and left hemiparesis. On operation no subdural hematoma was found, but an underlying subcortical hemorrhage on the right side was liberated through a ventricular needle. Convalescence was uncomplicated and the patient was reported well two months later.

Subdural Abscess

A prisoner of war was seen at the Regional Hospital in Monterey 2 June 1945. A week previously, while working at an unloading platform, he had been struck on the forehead by a heavy box and his nose was fractured. He was not unconscious. When signs of meningeal irritation developed, a specimen of spinal fluid was cultured but the report was negative. Right hemiparesis, aphasia and early papilloedema developed and a right-sided seizure occurred followed by stupor. At operation a left frontal subdural abscess was drained and the patient recovered.

Late Sequelae of Rheumatic Fever

In July 1944 a 23-year-old soldier was found unconscious in his car. He was admitted to hospital, where studies were unrevealing. He was then transferred to the General Hospital at Van Nuys, California, for further investigation.

He manifested occasional twitching movements of the right arm and leg, moderately dilated pupils unresponsive to light, and a slight divergent strabismus. The spinal fluid pressure was not elevated, there were three cells and the chemistry normal. Additional laboratory studies were non-contributory. The calcified pineal body was in the midline.

Bitemporal trepanations excluded a subdural hematoma, and a normal ventricular study excluded a ventricular or other kind of tumor. Several consultants examined him with no adequate conclusion being advanced.

After two months the patient died and at post-mortem examination well defined valvulitis of rheumatic type, with fibrinoid degeneration of the wall of the left auricle, was noted. There was no histologic evidence of embolism. There was, how-

ever, a non-hemorrhagic infarction with liquid necrosis, the result of pronounced endothelial proliferation of vessels in the pons. There was also a peribronchial infiltration resembling that found in rheumatic pneumonitis.

It was believed the pathologic changes were those of rheumatic obliterating arteritis with the chief involvement of the small blood vessels throughout the body and particularly the arterioles. Such were manifested by the endothelial hyaline bodies, rheumatic arteritis, and the severe degree of endothelial proliferation with complete occlusion of the arterioles.

Spontaneous Subarachnoid Hemorrhage

A 28-year-old woman with rheumatic heart disease developed aphasia, right hemiparesis, and coma. The spinal fluid was bloody and under pressure. The patient improved and then regressed following a Jacksonian convulsion before death. Spontaneous subcortical hemorrhage from a congenital or mycotic aneurysm was believed to have taken place. Postmortem examination revealed a ruptured aneurysm of the left middle cerebral artery with an associated encephalomalacia of the left temporoparietal area. There was obvious rheumatic endocarditis, but no indication of rheumatic encephalitis or embolism.

Subacute Bacterial Endocarditis and Emboli

A 27-year-old woman was seen in consultation in Santa Maria, California, 10 July 1946. During the first part of June in the latter part of her second pregnancy, she developed a right hemiplegia. She was examined by an ophthalmologist who noted hemorrhages in her eyegrounds, thought to be embolic in character. Gradually she improved, and on 27 June delivered a five-pound infant that lived 24 hours. Death was attributed to erythroblastosis foetalis.

The patient did well until 8 July, when a second hemiplegic episode occurred, followed by coma. No cardiac abnormality was diagnosed, and there was no indication of a placental neoplasm. The hemiplegia and coma were believed due to hemorrhage in the left frontotemporal region. A few days later petechiae indicative of emboli and endocarditis were evident over the body. Substantial amounts of penicillin were administered without beneficial effect.

Postmortem examination revealed a subacute bacterial endocarditis. An unidentified Gram-positive bacillus was cultured from the mitral valve vegetation. There was a focal embolic glomerulonephritis and recent and old infarcts of the spleen and liver. An encephalomalacia, associated with thrombosis of the left internal carotid artery was uncovered in the left cerebral hemisphere.

Myocardial Infarction and Emboli

Because of severe left flank pain, a 49-year-old mechanic was admitted to hospital in Santa Barbara, California, 17 May 1965. Subsequently he complained of chest pain, numbness of the left arm, and headache. The following day right hemiplegia developed and the patient became unresponsive.

When the patient was seen in consultation three days later, the spinal fluid pressure was normal and the total protein 67 mg per 100 ml. It was believed he had had a thrombosis or embolism involving the left middle cerebral artery. Diagnostically, acute bacterial endocarditis in the absence of a murmur or an atypical myocardial infarction with a mural thrombus and multiple emboli were considered. Arteriography the day of consultation revealed total occlusion of the left internal carotid artery just before the point of bifurcation into the anterior and middle cerebral branches. It was believed operative intervention was not indicated. The patient died 23 May.

Postmortem examination disclosed nonbacterial thrombotic endocarditis involving the mitral valve with multiple secondary embolic infarcts to the spleen, recent, and to the kidneys, old and recent, and embolic occlusion of the left carotid artery and its major branches. There was also acute encephalomalacia of the left cerebral hemisphere with pronounced edema. Additionally there was an hemorrhagic micro-infarction of the right cerebral peduncle and mid-brain. Sections from the posterior left ventricle revealed oxyphilic necrosis and recent microinfarction with focal loss of myocardial substance and infiltration by small numbers of histiocytes.

Spontaneous Subcortical Hemorrhage

A 30-year-old man suddenly developed thickening of speech, aphasia, right-sided convulsion, right hemiparesis and deepening coma. When seen in consultation he was critically ill. Temperature

was 105°F. The spinal fluid pressure was slightly elevated, but the fluid clear.

The suddenness of onset suggested a vascular accident, representing either a spontaneous subcortical hemorrhage or a hemorrhage into a tumor in the left frontotemporal area.

A ventricular needle inserted through a trephine opening in the left frontotemporal area liberated 80 ml of old blood. A few pieces of cerebral tissue removed with a biopsy needle revealed no tumor tissue, nor was any found in the collected blood.

The patient recovered and within a few weeks was able to return home. Speech instruction was started. A few months later his speech and right hemiparesis had improved considerably. A year later he had little residual disability. When last heard from he was doing well.

Fat Embolism

A woman 88 years of age sustained a cerebral contusion, fractures of the fibula and tibia and ribs on the left side in an automobile accident. Her condition deteriorated and she died nine days later. The possibility of fat embolism in addition to her cerebral contusion was considered, but the urine and sputum were not examined for fat. No emboli were seen in the optic fundi. At necropsy extensive fat embolization was noted in the lungs, heart, pancreas, kidney, brain and ovaries.

Meningitis

Pneumococcal

A 62-year-old man, injured in a fall from a dump truck, did not lose consciousness. When he was seen in consultation in Santa Maria, California, except for numerous abrasions about his face and body, the findings were not unusual. Skull radiographs revealed a stellate fracture into the frontal sinus on the right side.

A month later he was admitted, unconscious, to a hospital in Santa Barbara, California. It was assumed a subdural hematoma had developed. When examined, in addition to his comatose state, he had bilaterally positive Babinski reactions, but no stiffness of the neck and no paralysis or weakness of the extremities. Bilateral trepanation excluded subdural hematoma. The left lateral ventricle was tapped and a ventriculogram done. Fluid was sent to the laboratory to exclude meningitis. Penicillin was given preoperatively. The ventriculogram revealed no deformity. Death occurred

that evening. Pneumococci was grown from a culture of the ventricular fluid.

Tuberculous

Thirteen days after a fainting spell, a 52-year-old woman had onset of swelling of the right sternoclavicular articulation, viewed radiographically as an arthritic process. The swelling subsided in two weeks and she returned to work. Two days later she had a fever and after several more days she noted a right-sided numbness, which was followed by irrational episodes.

The patient was admitted to hospital, and when she was seen in consultation three days later, the salient features were coma, a temperature of 104°F, stiffness of the neck, transient nystagmus, dilatation of the right pupil, and bilaterally positive Babinski reactions. The urine contained a trace of protein, the blood cell count was normal, and the blood and spinal fluid serology negative. Tests for brucellosis and typhoid fever were negative. The spinal fluid pressure on the day of admission was 260 mm of water. There were 160 cells per cu mm, predominantly lymphocytes, the sugar content was 24 mg and the total protein 510 mg per 100 ml. Four days later, total protein was 744 mg and sugar 12 mg per 100 ml.

The patient was believed to have tuberculous encephalomyelitis. Beginning the day following admission to hospital and continuing for the next two weeks, 300 mg of streptomycin was given every three hours.

In the ensuing week spinal puncture was carried out at frequent intervals and the cell count was variable but largely lymphocytic in character. Reports on culture and guinea pig inoculations of spinal fluid were negative. No embolic tuberculous bodies were seen on funduscopic examination. The blood sedimentation rate was considerably elevated.

The patient did not regain consciousness, her condition deteriorated gradually and she died a month after entering the hospital.

The necropsy diagnosis was tuberculous leptomeningitis and tuberculous granular ependymitis. No demonstrable active focus of tuberculosis was found in any other part of the body and the pathologist conjectured that some microscopic focus in the brain had ruptured into the subarachnoid space.⁴⁵

Drug Intoxication

Bromides

A 60-year-old comatose woman who had a few weeks previously been discharged from another hospital after reduction of a fracture, was seen in consultation. Laboratory findings excluded diabetes and nephritis. The spinal fluid findings were normal. Fat emboli seemed precluded by the time interval. Diagnosis was established by blood bromide determination. The patient recovered uneventfully.

Barbiturates

A 56-year-old woman whose husband had died recently of cancer, was unconscious when seen in the intensive care unit of a hospital. General physical and neurologic examinations were not revealing. Results of routine urinalysis and blood studies were normal, as were spinal fluid studies. Stomach contents and urine were sent to the laboratory for drug determination. The patient regained consciousness in 36 hours and admitted taking 24 sodium amytal tablets because of depression over her husband's death.

Codeine

In 1963 a 29-year-old woman was seen in the intensive care department of a hospital. She was unconscious, had slow respirations and pin-point pupils. The spinal fluid findings were within normal limits. Stomach contents were saved for examination. Within 24 hours the patient recovered and admitted having taken 16 tablets of codeine.

As she had been in hospital for several weeks in 1954 because of a nervous breakdown and once in 1959 had taken a number of sleeping pills (although not enough to keep her from awakening the following day) she was referred to the mental health clinic.

Uremia

A 66-year-old man was admitted to the intensive care unit of a Santa Barbara hospital 14 July 1954. When seen in consultation he was in an oxygen tent. His pupils were constricted and his lips covered with blood. Urinalysis showed 15 to 30 erythrocytes per high powered field and a large amount of protein. Hemoglobin content was 10.8 grams per 100 ml of blood; erythrocytes numbered 3,620,000 and leukocytes 21,000 per cu

mm. There was no neck stiffness and no hemiparesis. The Babinski sign was negative. It was believed the patient had had some kind of cerebrovascular accident, difficult at this time to evaluate. The blood about the mouth suggested bleeding from esophageal varices or a gastric ulcer. There seemed no indication for diagnostic neurosurgical procedures and recovery appeared doubtful.

On a previous admission, in 1952, the patient had complained of fatigability and weight loss. The urine contained protein and occasional coarsely granular casts. The hemoglobin was 8.8 grams per 100 ml. At that time the impression was that of primary hypochromic anemia.

At 3 o'clock in the afternoon the day after the current admission, Cheyne-Stokes respirations developed and the patient died at 8:30 p.m. The salient features of the necropsy findings were those of subacute diffuse glomerulonephritis with fibrinous pericarditis and acute bronchopneumonitis. The cause of death was given as uremia with terminal acute bronchial pneumonia.

Cause of Death Not Clearly Established

On 30 June 1948, a Mexican man 25 years of age had an episode of vertigo while working on a construction job in a temperature of 107°F. About 5 p.m. one of his friends found him unconscious and took him to the emergency department of one of the Santa Barbara hospitals.

On physical examination clonic movements of the right arm and leg, pupillary dilatation, and occasional episodes of carpopedal spasm, associated with irregular breathing and cyanosis, were noted. Rectal temperature was 104°F. Leucocytes numbered 25,000 per cu mm, with accentuation of the neutrophilic elements. Some improvement followed the administration of a unit of plasma and calcium gluconate. According to a member of the family the patient had always been well, had had no seizures, and had been in the Navy seven years.

While heat stroke was considered along with other impressions, a convulsive disorder of undetermined cause seemed the logical diagnosis. The patient died the following morning.

The pathologist believed the anatomic findings of the postmortem examination were insufficient to explain death. The history of hyperpyrexia and convulsions were believed consistent with death from heat stroke.

Phycomycosis (Mucormycosis) of The Central Nervous System

A 30-year-old woman, known for six years to have diabetes, had sore throat, nausea, vomiting, and confusion. The confusion cleared and was followed by lethargy and impaired movement of the left eye. Diabetes, at first believed the cause, was found to be under control. The spinal fluid pressure was normal and it contained 12 cells per low power field. On one occasion leukocytes numbered 37,000 per cu mm and on another 24,000. Blood cultures were negative. Evidence of a mild sinusitis was noted on x-ray films. The patient said she had noticed that if she had too little or too much insulin her eyes would tend to deviate.

While she was under observation, weakness of the left arm developed and unconsciousness ensued. She was admitted to a hospital in Santa Barbara for diagnosis and treatment.

On ophthalmoscopic examination, startling pallor of the optic fundi was observed, which was attributed by the consultant to complete obstruction of both central retinal arteries. There was also left lateral rectus paresis, impaired movement of the right arm and leg, and bilaterally positive Babinski reactions.

Medical consultation suggested an infectious process, probably of respiratory tract origin. Diabetic coma was excluded. Leukemia was not confirmed by laboratory findings, and nothing was observed on cardiac examination to indicate an embolic process.

Because of the probability of infection, substantial amounts of antibiotics were given. Within 24 hours necrosis of the lids and the globe of the left eye had occurred. This was believed consistent with retrograde thrombosis of the ophthalmic artery bilaterally. The importance of culturing biopsy scrapings was not appreciated. The patient died two days after admission to hospital.

Postmortem examination revealed basilar fibrinopurulent lepto-meningo-encephalitis with thrombosis of the left anterior and middle cerebral arteries as well as the intracranial portion of the left internal carotid artery. There was also bilateral cavernous sinus thrombosis, thrombosis of the superior longitudinal sinus and bilateral thrombosis of the ophthalmic arteries. Additionally there was acute suppurative ethmoiditis and sphenoiditis, as well as cellulitis of the orbits, the retro-orbital tissues and periorbital skin.

Bacterial studies were non-productive. Unfortunately no cultures were made for yeasts or molds, but microsections of tissue blocks from the brain, retrobulbar structures, internal carotid arteries and cavernous sinus, stained with Hotchkiss-McManus technique, revealed myriads of molds exhibiting abundant coarse and non-septate mycelium. The fungus was identified as a phycomycete by the Armed Forces Institute of Pathology.

Discussion

Not infrequently a comatose patient is brought into an emergency department with little previous medical information or evaluation. The history from relatives may be incomplete or conflicting, or there may be none available. A language difficulty may add to the confusion. In the largest single group of such cases, those due to suicidal attempts with depressant drugs, misguided efforts by friends and families often conceal the facts.⁶ Not uncommonly precipitous deterioration leads to consultation, but too late for appropriate treatment.

Preliminary examinations and laboratory findings may fail to supply the solution ordinarily anticipated. Such situations present a diagnostic challenge. Neurological surgeons are often consulted in undiagnosed and unusual cases.²

Certain therapeutic measures—clearing an airway, controlling bleeding and shock—take precedence over diagnostic procedures.^{1,2,4} The possibility of a fractured cervical spine demands caution in movement of the head and neck to avoid injuring the spinal cord. Hypoglycemia, a common and serious cause of metabolic coma, can bring about various combinations of signs and symptoms. It is therefore important to draw blood for sugar determination and then to administer 25 grams of glucose intravenously. The injection can do no harm and is enough to protect the brain against hypoglycemia until the result of the blood sugar determination is available.⁶

The situation in which the patient is found may be relevant or it may be misleading. One unconscious with head injuries may have been knocked down or may have fallen as the result of a cerebrovascular accident. An alcoholic breath does not necessarily mean coma from alcohol.¹

The examination should be rapid but thorough. All indicated laboratory examinations and diagnostic procedures are essential.³ A lumbar punc-

ture may immediately establish the presence of subarachnoid hemorrhage or meningitis. Arteriography will be diagnostic of subdural or other space-occupying lesion. These problems are best solved in an intensive care facility by those experienced and available to work together.^{5,7}

Cerebral vascular insufficiency resulting from thrombosis, arteriosclerosis or an expanding lesion requires differentiation by means of neurosurgical diagnostic procedures. In many instances the possibility of an expanding lesion has to be excluded.

Recovery of pregnant patients following removal of parasagittal meningiomas in unpromising situations has been reported as unexpected.^{8,9,10}

Cases of subdural hematoma have been reported during anticoagulant therapy.¹⁷ When such lesions are suspected and the patients seriously ill, trepanation may well be preferred to angiography, as it is almost without complication and also treats the lesion.⁶

The second patient with an unsuspected subdural hematoma reported herein had been treated for hypertension. It was believed advisable to exclude an expanding lesion. Arteriography would have established the diagnosis of the uncommon subdural hematoma resulting from the rupture of an intracranial vascular anomaly.^{11,12,14,15}

The last of these cases was interesting diagnostically because the coma was logically believed to be due to hepatic insufficiency. The pupillary abnormality was consistent with the addition of a subdural hematoma.⁶ The almost terminal evacuation of the hematoma failed to lead to recovery.^{16,50,51}

Often symptoms of a subcortical hemorrhage simulate those of a subdural or epidural hemorrhage and may be associated with them.^{18,20} Arteriography has been diagnostically important.³⁴ Before its use, when a subdural hematoma was not uncovered, tapping for the presence of a subcortical hemorrhage has proved important, as it was in the case herein presented. With the addition of cerebral contusion and other hemorrhage, prognosis is grave.^{35,36} Courville and Blomquist¹⁹ considered subcortical hemorrhage the result of one of three processes: the development of foci of necrotic softening as a direct result of the trauma, preexisting alterations in the vessel walls, or delayed hemorrhage in a focus of primary hemorrhage occurring at the time of injury.

In many ways the clinical manifestations of subdural abscess resemble those of subdural hema-

toma. Courville and Blomquist²¹ found infection of the subdural space an uncommon lesion following injury. It occurs by direct implantation, by extension from traumatic cellulitis or an infected wound, or secondarily by traumatic osteomyelitis of the skull. It may also be a complication of an intracranial aerocele, traumatic sinusitis, traumatic otitis media or mastoiditis, or traumatic rupture into the subdural space of a brain abscess. The diagnosis should be suspected in a comatose patient with a history or x-ray findings of rhino-otitic infection.

Insofar as the late sequelae of rheumatic fever are concerned, the diagnosis in the case herein reported was made at necropsy. An intracranial expanding lesion was necessarily excluded. Several consultants were unable to offer a diagnosis. It is doubtful that angiography, not commonly done at such a time, would have been helpful.

Attention has been directed to the occurrence of cerebral rheumatic obliterating arteritis in persons with rheumatic heart disease.^{22,23,24,25} This late sequela of rheumatic fever involves mainly the small meningeal and cortical vessels producing gross or microscopic softenings in the cortex. It may occur from several months to many years after the acute stage of rheumatic fever and at a time when the patient is otherwise well. That such can lead to an undiagnosed case of coma is evident from the above experience. In contrast, the patient with rheumatic heart disease died of rupture of an aneurysm of the left middle cerebral artery without indication of rheumatic encephalitis or embolism. Arteriography would have visualized the aneurysm, but in view of the patient's condition and cardiac disease, its omission seemed reasonable.^{26,27}

While unconsciousness and death from subacute bacterial endocarditis and emboli may seem neurosurgically far afield, the initial problem in the case presented was that of hemiplegia and coma, apparently from hemorrhage into the left frontotemporal region. The fact that hemorrhage in the eyegrounds, believed embolic in character, had been noted should have led to additional diagnostic tests. Manifestations of the petechial hemorrhages established the diagnosis, but earlier recognition and treatment might have led to survival.

Bacterial endocarditis is productive of a variety of clinical symptoms, some pursuing a rapid and acute course, others evolving slowly over a period of months.^{29,30,31} Depending upon the prominence

of the various manifestations, the diagnosis of subacute bacterial endocarditis may be easy or difficult. A wide variety of microorganisms, including nonpathogenic bacteria, may produce subacute or acute bacterial endocarditis. The subacute variety caused by the streptococci of the viridans group is the most common.

The case of myocardial infarction with mural thrombosis and systemic embolism seemed atypical in its manifestations. Arteriography, revealing a total occlusion of the left internal carotid artery just before the point of bifurcation into the anterior and middle cerebral branches was diagnostically helpful.

The patient with spontaneous subarachnoid hemorrhage recovered following liberation of blood by a ventricular needle. No arteriography was performed, but the critical condition of the patient justified immediate trepanation and drainage.^{27,28,32,33}

The case of fat embolism was one associated with cerebral contusion and fractures of the long bones.^{38,40} The condition may occur in association with blunt trauma to adipose tissue, or rupture of certain viscera rich in fat, such as the liver, and it may also follow abdominal operations. Fatal cases have been reported after slight trauma. It occurs in a high proportion of injuries but infrequently manifests itself in sufficient severity to lead to obvious symptoms and recognition. It is probable that many cases of fat embolism go unrecognized and the patients recover.

Warthin⁴² in 1913 called attention to fat-containing alveolar cells in the sputum as a diagnostic laboratory test, and Scriba⁴¹ in 1880 reported fat in the urine after fractures. In 1929, Oppenheimer³⁹ described fat globules in the retinal vessels in fat embolism.

On the other hand, Fuchsig and his associates³⁷ felt such findings were unreliable. They believed diagnostically the important factor was an awareness that fat embolism often exists in cases of mild as well as in severe trauma. The symptom-free interval they found a characteristic feature. They were of the opinion that treatment lay not in the administration of special drugs, but rather in adequate supportive therapy for traumatic shock.³⁷ The discovery of a more definitive laboratory test would be diagnostically important.

In the case reported herein of pneumococcal meningitis following a stellate fracture into the frontal sinus on the right side, the condition was

probably masked by antibiotics given after the injury. The patient had been seen in consultation on one occasion. Coma occurred three weeks later. A spinal puncture might have established the diagnosis and obviated the cranial procedures. At the time, however, there was no stiffness of the neck, and the exclusion of a subdural hematoma seemed necessary.

It has long been known that the onset of tuberculosis meningitis may be insidious and the symptoms mild, which increases the difficulty of early diagnosis.⁴⁴ While choroidal tubercles are present and visible as ill-defined, yellowish bodies in about 50 percent of the patients, they are usually overlooked.⁴³ In some 27 percent of cases, chest radiography has revealed miliary dissemination. A pleocytosis of mononuclear and polymorphonuclear cells occurs, with the former predominating. The protein is variably increased, and the chloride and sugar content of the fluid much reduced. The tubercle bacilli are infrequently found in the fluid, and while demonstration of them clinches the diagnosis, their absence is of less significance. In doubtful cases guinea pig inoculation should be used.

Before the advent of streptomycin and isoniazid, there was no effective therapy. With present treatment adults fare less well than children.⁴⁶ Cures of 80 percent have been reported in children up to ten years of age, but in only 14 percent of patients over 40.⁴⁶

Alcoholism and drug intoxication are frequent causes of coma. Alcoholism is often associated with an unsuspected subdural hematoma. Because of concealment or ignorance of its cause, the diagnosis of drug intoxication may at first be disconcerting. The importance of gastric lavage and laboratory tests in the diagnosis is obviously important, as is appropriate treatment. The use of antagonists has been considered valuable by many.^{47,48,49}

As Bright reported in 1817,⁵³ the indications of uremia may be protean. Appreciation of its manifestations would have led to an appropriate diagnosis in the case herein reported. Normochromic and normocytic anemia is almost an invariable feature. Both depression of erythropoiesis and an intracorpuseular hemolytic component are thought responsible.⁵² In terminal renal failure pericarditis occurs with frequency. Ulcerative lesions of the gastrointestinal tract, especially in the mouth, add to the patient's discomfort. Bleeding from the

mucous membranes of the nasopharynx, the stomach and the small or large bowel is a common terminal complication. Renal failure may be associated with symptoms referable to the peripheral and the central nervous system.^{53,54}

As to heat stroke, although the postmortem findings in the pertinent case reported herein were believed insufficient to explain the cause of death, the history of hyperpyrexia and convulsions was felt consistent with death from heat stroke. The significant findings are prostration and pyrexia. A rectal temperature of more than 106 degrees is a grave prognostic sign. Management of the condition requires heroic measures. While an ice-water bath seems drastic, there is no effective substitute. If the temperature falls below 103 degrees, the bath should be resumed in event of recrudescence.^{55,56,57}

Importantly again, a knowledge of the uncommon clinical features of mucormycosis could lead to its diagnosis and treatment. Such should be borne in mind in patients with debilitating disease, in those receiving antibiotics, steroids or anti-tumor agents, and particularly in those with diabetic acidosis. Even in the presence of an aroused clinical suspicion, the progression of the disease is often so rapid that administration of fungicidal therapy does not lead to recovery. Moreover, recovery, if achieved, is usually at the expense of disabling disabilities. With the advent of amphotericin B, the prognosis, once invariably ominous, has brightened somewhat.^{58,59,60,61}

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The Treatment of Superficial Fungous Infections

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■ *Superficial fungous infections of the skin often are difficult therapeutic problems especially if the laboratory identification of the organism, necessary to guide selection of means of treatment, is not obtained. Proper diagnosis will reveal that some infections need certain specific antifungal drugs topically applied, another group will yield to other less specific topical therapy, and a third type can be successfully influenced only by oral administration of griseofulvin.*

FUNGUS DISEASES of the skin are considered to be difficult therapeutic problems by the majority of practitioners of medicine. It is impossible for even the most extensively experienced physician to distinguish fungous infections from non-fungal disorders solely by visual examination of the lesions, but in the vast majority of cases the distinction can easily be made by direct microscopic examination of bits of tissue from the affected site. This technique is easily learned and the examination can be quickly performed. Culturing methods are also used by most dermatologists, mainly because identification of the species of fungus is of great value in prognosis and in epidemiology.

A few general rules by which treatment should be guided must be emphasized. The stage of the disease process must also receive consideration. Strong medications should not be used on acutely inflamed or vesicular areas, nor around eyes or perineum. Secondary infection with pyogenic bacteria is often superimposed on fungous disease, and

must ordinarily take precedence in selection of treatment. Allergic reactions to fungal products or to medications often cause added trouble.

Tinea versicolor is the most superficial of all cutaneous fungous infections, and one of the commonest. In some areas of the world, mainly those which are hot and humid, more persons are infected than are free of it. The causative fungus is larger than other species and is easily seen microscopically as short curved hyphal fragments and groups of globular budding cells. There is usually no inflammation or other symptom, but only an objectionable alteration of the degree of pigmentation of the involved spots, which are either darker or lighter than the surrounding normal skin, according to whether the infection causes the scales to be shed more easily or abnormally retained. Ultraviolet radiation causes a fluorescence which can be helpful in determining the site of lesions and the progress of treatment.

Because it is so superficial, tinea versicolor is very easily treated. Any antifungal preparation usually gives good results. In many cases large areas of the body must be covered, and frequently several members in a family are involved. Many persons are so susceptible that they become reinfected soon after the lesions have cleared. For

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these reasons it is well to remember that simple and inexpensive remedies can be effective. Sodium thiosulfate, 20 percent in aqueous solution with perhaps 10 percent glycerine and 10 to 20 percent isopropyl alcohol, will serve if applied daily at first, then twice weekly until the lesions are cleared. It need be left on only during sleep and can be removed by a morning bath that will wash away most of the sulfide odor which is often objectionable. Several proprietary preparations are popular. Griseofulvin by mouth is totally ineffective.

Moniliasis (Candidiasis) is very frequently encountered in a mild superficial form, particularly in intertriginous areas of the body under climatic conditions causing excessive perspiration. *Candida albicans* needs some such abnormality to become pathogenic for human beings. Other similar contributing conditions arise from prolonged maceration through contact with wet materials such as those handled by cooks, dishwashers, pie-makers, salad-makers or housewives. *Candida albicans* can also become the cause of deeper infections of the skin, mouth and vagina, and even of a serious disease of internal organs in persons afflicted with systemic abnormalities such as diabetes, leukemia, malignant proliferation, nutritional or vitamin deficiencies or those produced iatrogenically in attempts to treat such disorders by administering antimitotic, antibiotic, immuno-suppressive, corticosteroid drugs or roentgen radiation.

The most important factor in therapy is the discovery and control, wherever possible, of all contributing factors such as those named above. The maintenance of dryness in the affected areas of the skin is extremely helpful, often even curative, and is best accomplished by occasional cleansing with an astringent such as Burow's solution, followed immediately by complete air drying and the application of plain talc as frequently and liberally as needed. Powders containing starch must be avoided, for starch when moist feeds *Candida*.

Nystatin or amphotericin B are effective antifungal drugs specifically against *Candida*. They may be applied thinly as lotion or cream to involved areas, then allowed to dry in air, and the area powdered. For oral lesions, aqueous solutions or troches must be held in the mouth for a time—troches until they disintegrate—before being swallowed. Griseofulvin is not at all effective in candidiasis, and often proves harmful.

Candida albicans frequently causes chronic paronychia or onycholysis in food handlers. It is

necessary, even though difficult, to maintain dryness for several weeks while the abnormal clefts or interstices are repaired by the outgrowth of the nail. Thymol, 2 percent to 4 percent in chloroform, has been recommended for use three times a day and after each exposure to moisture.

Dermatomycosis

Somewhat more than half the pathogenic fungi attack only the epidermis, unless they are affected by an associated bacterial infection or allergic sensitization. The resulting disorder is widely called tinea or ringworm although *dermatomycosis* is the term much to be preferred. All these terms are conveniently classified further by an adjective indicating the region involved, since there are resulting important variations in diagnostic and therapeutic procedures.

Tinea capitis occurs in several forms, varying according to the causative fungus. Characteristic of all types are rounded patches in which the hairs break off. The two commonest types are limited to prepubertal children: one is acquired from animals such as cats and dogs, the other is transmitted from child to child in epidemic fashion.

Determining the type, which can be done accurately only by culturing, is valuable epidemiologically and for prognostic reasons. In both types the involved hairs fluoresce brilliantly under ultraviolet light, a distinct aid in diagnosis, a guide to treatment, and the easiest criterion of cure.

Tinea capitis is difficult to cure by topically administered antifungal drugs because the fungus invades the follicles deeply and, by proliferation, fills them with dense masses of spores which no medication penetrates.

The advent of griseofulvin in 1959 provided systemic treatment. This agent when orally administered enters the blood and is incorporated in the newly forming epidermal cells of the skin and hair bulb, enabling them to resist the penetration of the fungus during all of their outward growth. Dividing the dosage during the day and after meals of a diet as high in fat as tolerable enhances the absorption and efficacy. For adults a total of 1 gram daily of the earlier preparation or 0.5 gram of the "finely divided" form is usually sufficient. For children the dose can be reduced, but never below 0.25 gram daily.

Because the action of griseofulvin is from within, and is largely only fungistatic, the ultimate cure depends on the cells involved with fungi being

pushed exteriorly enough to be shed finally as scales, or clipped away from hair or nails. Thus the length of treatment depends on the time necessary for this process to be completed, and will vary from two weeks for truly superficial tinea corporis to a year or more for slow-growing great toe nails. It is at once evident that for the latter more difficult cases microscopic confirmation of a fungal cause is absolutely necessary before embarking on so long a program.

Tinea barbae, which is rare in this country, closely resembles tinea capitis in prognosis and treatment.

Tinea corporis occurs on the trunk and extremities, usually as a few rounded plaques with actively progressing, erythematous, vesicular borders, leaving clear centers. As the follicles in the areas affected are not deep, disease remains superficial and is easily cured. Therapy with any mild fungicide such as 3 percent each of sulfur and salicylic acid in an emulsion base is usually effective within two weeks.

Tinea cruris and tinea in the perineal and perianal areas are less common than generally believed and are especially difficult to differentiate from a host of other diseases. Laboratory confirmation must be obtained before treatment is begun, because griseofulvin by mouth is effective provided the infection is due to a dermatophyte, but it is useless and at times even harmful for candidiasis, which cannot be differentiated clinically.

Tinea pedum exists in several forms, varying from acute to chronic. Since fungi are responsible for considerably less than half the cases of dermatitis involving the feet, accurate laboratory con-

firmed of the presence of fungi is of inestimable help in therapeutic management.

Many cases of the acute vesicular variety are easily controlled by maintaining dryness and by topical use of any of several antifungal preparations. However, for the extremely chronic, dry, hyperkeratotic form of tinea pedum, topical therapy is almost completely useless. Griseofulvin by mouth is often curative, and it will help at least to some extent in all cases. Some persons are so exquisitely susceptible to infection of this type caused by *Trichophyton rubrum* that they either do not become entirely well or soon become reinfected. Even so they often welcome the degree of help afforded by griseofulvin.

Tinea of the nails is always difficult to cure, for the actively progressing border of the disease is so shielded by the impervious nail that medication cannot reach the fungi. Griseofulvin will cure many cases, but the drug must be taken for six months and often much longer.

The role of topical antifungal preparation has been decidedly reduced by the advent of griseofulvin. However, frequent bathing may dissolve the drug out of the most superficial keratin layer, leaving viable fungi there (after cure has apparently been obtained) which can immediately penetrate more deeply and masquerade as reinfection. In such circumstances topical application of a fungicide appears warranted. Whitefield's salicylic-benzoic acid ointment or any one of many proprietary remedies is effective; in fact mild ringworm of the non-hairy skin and the common form of acute infections of the feet often can be treated successfully with such preparations without the help of griseofulvin.

The Catheter

How to Use and When Not to Use

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■ *Catheterization should not be used without true indication. Careful control of hydration, sedation, anesthesia and use of anticholinergic agents before, during and after operation can do a great deal to prevent the need for catheterization. When the procedure is necessary, simple, inexpensive measures of care usually are sufficient. Prophylactic antisepsis before and after, with reexamination of the urine after discontinuance of antiseptic drugs to make sure there is no recrudescence, prevents acute and chronic infections.*

The catheter recommended for routine male and female catheterization is the 14-16 (French) olive tip coude (Tieman) catheter or the Tieman-Foley.

Closed drainage systems are the best. Continuous irrigation is without value. Water is an excellent irrigant. Calcium deposits are prevented by Renacidin® instillation and acetic acid irrigation.

MUCH HAS BEEN SAID and written about morbidity and possible lethal sequelae of urethral catheterization, and while it is true that problems can arise incidental to urethral instrumentation, for the patient who cannot void urine spontaneously, the benefits far outweigh the faults.

As physicians, we must do all we can to prevent the conditions necessitating catheterization; but since the procedure is sometimes necessary we should teach ourselves and assistants the indica-

tions and contraindications, the proper types of catheters and the techniques of using them. Prophylaxis against infection before, during and after catheterization must be emphasized.

Lest they be passed over in the recent welter of reports by internists, bacteriologists and urologists emphasizing new and costly methods of catheter care, good inexpensive ways to serve those purposes are described in this communication.

Indication

The prime indications for vesical catheterization are: (1) to empty a full bladder with complete retention; (2) to withdraw urine from a partially

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full bladder, with or without infection, for diagnosis or cytography, for relief of lower obstructive uremia or for alleviation of symptoms; (3) to ascertain the presence or absence of infection after bacilluria or pyuria is noted in a voided specimen; (4) to dilate urethral strictures; (5) to drain the bladder after operation on or around the bladder or prostate; (6) to drain the bladder and splint the urethra after surgical treatment of the urethra; (7) to retain ureteral catheters exiting from the urethra; (8) to collect data for research purposes; (9) to determine whether true oliguria is present and to monitor output; (10) to be prepared for retention, as after abdomino-perineal rectal resection.

Contraindication

Vesical catheterization should not be done (1) to determine the presence of infection until after voided urine collected by the two-glass or three-glass technique has been examined; (2) in the presence of acute prostatitis, unless there is complete urinary retention; (3) on routine order for catheterization *pro rata necessitatis*, except where there is true indication for the procedure.

Preventing the Need for Catheterization

In most situations, proper collection, prompt delivery to the laboratory and immediate examination of spontaneously voided urine obviates the need to obtain specimens by catheterization for accurate bacteriologic study. However, regardless of how obtained, prompt examination is mandatory, in light of the fact that bacteria in the specimens double in number every 20 minutes.

Anticholinergic agents, including antihistamines and atropine-like drugs, decrease the power of the vesical detrusor. Sympathomimetic drugs may place the detrusor at a disadvantage. This sometimes occurs without preexisting obstruction, and it is common where organic block is present. Therefore, use of these drugs should be avoided or held to a minimum in patients with urethral obstruction, especially surgical patients.

Whatever the operation, the patient should void before receiving preoperative medication and before going to the surgical suite. The anesthetist should use only enough intravenous fluid to keep the needle open and to replace calculated fluid loss. Anesthesia should be gauged so that it will not continue long after operation, for it is impor-

tant that the patient become aware of the filling bladder and initiate urination as early as possible lest long retention cause decompensation of the detrusor. For this reason spinal anesthesia should be avoided if possible. With general anesthesia relaxation is obtained as needed by use of curare-like drugs with or without tracheal intubation. Also to prevent long retention, postoperative sedation should be held to the serviceable minimum. The patient must be able to get up and stand or to sit on a commode to urinate during the first 12 hours.

Orders for routine catheterization should not be given. It must be borne in mind that if a patient does not urinate the reason may be no more sinister than simply that he has so little urine in the bladder, he has no need to void. Lest severe retention be suspected in such cases, interns, nurses and nurses' aides should be carefully instructed in suprapubic percussion to determine whether the bladder is full. If the patient is awake and alert, questioning him can be helpful. When there is no dullness on percussion and the patient says he has no desire to urinate, catheterization is not needed.

Simple, traditional methods can be used to promote spontaneous urination. External warm douches or hot sitz baths will help.

The use of cholinergics is theoretically sound, but one ought not wait long for success after such drugs are given. The decompensated detrusor does not respond in physiologic manner, but drugs may be helpful in restoring function to the vesical detrusor.

Types of Catheters

There are several varieties of catheters that can be recommended. These are: the 14 or 16 (French) olive tipped coude (Tieman) plain or Foley catheter with a 5 ml bag; the olive tipped or regular 14 to 20 (French) with 30 ml bag; the regular Foley 14 to 18 (French) with 5 ml bag; the short tipped Foley 18 to 24 (French) regular with 5 ml bag; the 8, 10, 12, 14 (French) plain or Foley coude (Tieman) or regular Foley for infants and children. (See Figure 1.)

The best catheters for intermittent or indwelling use both in men and women are the olive tipped coude (Tieman) variety. They are shaped for the male urethra, but they easily enter through most obstructions and the sphincter in both sexes. They are firm enough to permit accurate direction of a considerable length of tubing. If a technician has difficulty in passing a No. 14 coude olive tipped



Figure 1.—Ideal catheters. Left to right, olive tipped coude types (which are best), whistle tipped plain, standard Foley, two short tipped Foleys and 30 ml bag Foley.



Figure 2.—Technique of injection of water-soluble lubrication or local anesthetic into urethra.

(Tieman) catheter, he should abandon the effort and call a physician.

Catheters with 30 ml bags are used for unruly patients. To prevent their forcibly extracting the tube, and possibly injuring the urethra in doing so, the bag should be inflated to 40 or 50 ml.

After initial catheterization with coude types, subsequent catheter replacement is easy. The No. 16 to No. 18 (French) regular catheter may be placed in males or females for long-term use.

Special types of catheters, bougies, guides and surgical catheters, are not presented here, but it should be noted that if they are needed a urologist should be called in. The same applies to the suprapubic catheter. The short tipped regular Foley 18 to 24 (French) is better if suprapubic catheters have to be changed by technicians. Catheters of the types used in various situations for adults can be used for children also, except that the smaller sizes are not made in the coude manner.

Technique of Catheterization

Asepsis is a necessary part of catheterization procedure. Soap and water is adequate for cleansing of the penis or vulvae. Simple antiseptic solutions should be applied about the meatus with cotton or gauze swabs. Eye sheets are best for draping the area but a single towel can be made to serve. Sterile gloves should be worn. Unless the table-side tray is so designed that instruments can be selected quickly, an assistant is needed. Sometimes in the catheterization of women an assistant must retract the labia to insure continuous view of the urethral opening.

Local anesthesia, although not necessary, may be helpful if the patient is apprehensive. For men



Figure 3.—For female patients, putting reversed bed pan under buttocks directs perineum anteriorly and makes urethra easily accessible.

a lidocaine (Xylocaine®) jelly introduced into the urethra is best for this purpose. Aqueous cocaine, 5 percent, applied to the urethral meatus is recommended for women, although lidocaine does fairly well and does not entail the hazard some observers attribute to cocaine. Cocaine should never be used for men because of the possibility of dangerous absorption along the relatively long urethra.

In male catheterization, lubrication is the most important single item. For this a Luer syringe, without the lock, is filled with water-soluble jelly and the tip is introduced into the meatus. About 10 ml of jelly is injected into the urethra (Figure 2). The coude (Tieman) catheter then will pass easily in almost all patients. If it does not, a urologist is needed. For females the catheter tip is generously smeared with a lubricant before it is inserted.

After placement of the catheter a bladder syringe (preferably with a 2-ounce rubber bulb) is used to

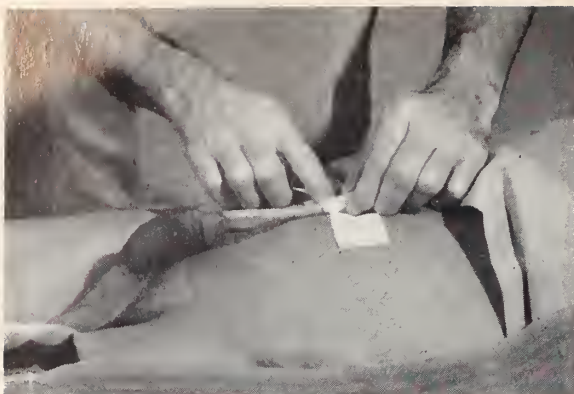


Figure 4.—If tape must be used, tape catheter cephalad and over thigh.

aspirate the tract to keep the lubricating jelly from blocking the catheter.

The position of the patient is more important in females than males. For males, the supine position in bed is adequate. In some females, even with abduction of thighs and flexion of the knees, the urethral opening may be difficult to see. In that case putting a bedpan upside down under the buttocks will turn the perineum upward (Figure 3). Even then, an assistant may be needed to spread the labia to enable direct visual access to the urethra without contamination. Good lighting is necessary.

In all cases without exception, regardless of the reason for catheterization, the amount of urine obtained at each voiding must be measured and recorded. If there is any doubt about the presence of infection, some of the urine should be collected in a sterile bottle for laboratory study.

The Foley balloon is inflated with 7 or 8 ml of water. Air should never be used, for it can escape unseen. If only 5 ml of water is injected, the bag is not adequately inflated and in females it may pull out of the bladder while in males it may pull out but lodge in the urethra at the point of passage through the prostate, causing pain and failure to drain. The arm of the balloon conduit should be folded back and secured with a rubber band and tape to prevent leakage at the valve.

The catheter should be connected to closed drainage collection devices. If it is to be secured in place by tape, women should have the tubing laid over the thigh so they can see it and protect it, and for men the penis should be turned cephalad to avoid abscess formation at the peno-scrotal angle (Figure 4).

Suprapubic Catheterization

Suprapubic catheterization, which is to be done only by persons trained in the procedure, should be reserved for use mainly when urethral intubation cannot be accomplished or when there is need for special bacteriologic information under research conditions. The instruments available are the standard spinal needles, small trochar needles and the suprapubic punches that are so designed as to permit placement of a catheter. The technique requires that the bladder be full, as determined by percussion. Local anesthesia is sufficient.

Prophylaxis

If preventive measures to forestall catheterization fail and the procedure becomes necessary, prophylaxis against possible infection is advisable. Culture and sensitivity tests, theoretically indicated to determine what drug to use take time and cost money. In lieu of such determinations a polyvalent oral antiseptic agent, either chemical or antibiotic, can be used. Subsequent choice of agents to prevent pyelonephritis and decrease the bacterial count in the bladder can be made empirically. In long-term catheterization, antiseptic agents help prevent deposits of calcium on the catheter. Other prophylactic measures when vesical drainage must be continued for a long time include low calcium intake, acidification, dilution of the urine, and frequent change of position by the patient.

Care During and After Catheterization

Rules for care of catheterized patients vary according to sex, the duration of intubation and whether the catheter is placed urethrally or suprapubically.

In both sexes, the drainage tube should lie across the thigh to insure protection and accessibility. Taping to hold it in place usually is not necessary, but if circumstances make fixation advisable the catheter must be cephalad in males to protect the peno-scrotal junction from pressure (Figure 4).

Urethritis is common with use of an indwelling catheter in males, and care must be taken to prevent damage from this complication. The meatus and the catheter must be cleansed several times daily to prevent crusting and obstruction. Application of various ointments about the meatus may be helpful. Hot sitz baths or hot wet packs once or twice daily help to prevent or to clear urethritis.



Figure 5.—Open Y breaks siphon. Elevation above bladder allows partial filling and relieves bladder spasm.

A good pack can be made of two bath towels, immersed in hot water and wrung out. After wax paper has been placed under the buttocks to protect bedclothing, the towels are wrapped around the genitalia and catheter (with penis pointing cephalad). With a hot water bottle placed on the towels and an old bath blanket covering all, the pack will stay warm for 30 to 40 minutes.

In females, external and internal warm douching with plain water prevents or relieves labial and urethral irritation and lessens the likelihood of ascent of infection through the urethra.

The fistula of the suprapubic catheter must be cleansed daily with soap and water. Application of silver nitrate prevents exuberant granulation about the fistula. A small surgical gauze pad should be placed around the tube at the point of entry and changed daily.

For bladder pain and bladder spasm, which may occur during the first day or two, rectal suppositories containing 50.0 mg of opium and 15.0 mg of belladonna provide relief. Intermittent drainage



Figure 6.—Intermittent bladder irrigator. Commercial disposable equipment is available.

may be necessary for relief of pain. Interposing a Y glass in the drainage system permits breaking of the siphon from time to time as necessary; and if the Y is elevated well above the bladder, partial distension is maintained, which prevents spasms (Figure 5). Use of a chemical dye so that the patient can "see what goes on" may have some psychological effect.

For continuous drainage, equipment should be of the closed variety. Three-way catheters with continuous irrigation-drainage devices are ineffective. For proper irrigation when three-way catheters are used, the outflow must be alternately clamped and released three times every hour to distend the bladder.

One-way intermittent irrigation equipment, without the continuous inflow, works very well. This is used mainly after operations on the bladder or prostate. The outflow of the Y is clamped and inflow released to allow the bladder to distend enough to hold 100 to 150 ml. Then the bladder is allowed to drain and the procedure is repeated



Figure 7.—Two-ounce glass plunger syringe. Inject and aspirate vigorously to evacuate clots.

two or three times (Figure 6). If there is active bleeding, irrigation must be done frequently. Should clots form, brisk in-and-out irrigation with a 2-ounce glass plunger syringe must be carried on until all clots are evacuated (Figure 7).

For ambulatory patients, in or out of the hospital, intermittent drainage or constant drainage into a leg bag is used. A device for intermittent drainage can be provided simply by doubling the outside tip of the catheter on itself, placing a clothespin to maintain the kink and fastening the clothespin to the underwear with safety-pins to prevent sitting on the tube (Figure 8). By opening the jaws of the clothespin and straightening the kink, urine can be released as necessary.

A patient with a catheter arranged for intermittent drainage must be cautioned never to sit in a bathtub or sitz bath with the catheter open and never to permit the end of the catheter to dangle into the toilet bowl.

Simple water is the cheapest liquid for irrigation, and a very effective one. Saline solution or distilled water costs more without much known additional benefit. Adding an antiseptic agent to the solution may help. As the aim of irrigation is to cleanse, distension of the bladder with four-ounces of fluid several times at each irrigation is good practice to provide the positive aspiration necessary for extracting debris from the bladder. The best instrument is a 2-ounce rubber bulb syringe with a strong bulb. If clots are present a 2-ounce glass plunger syringe should be used, with forced injection and strong withdrawal applied alternately until they are cleared. It must be borne in mind, however, that in some situations, such as following repair of vesicovaginal fistula, irrigation must not be too aggressive.



Figure 8.—Clothespin clamping catheter, permitting ambulation.

Patients requiring long-term catheter drainage must be observed for calcium deposits and vesical calculi. The catheter should be changed the first time after it has been in place one to two weeks. If no lime is present, the catheter may then remain in place for three to four weeks and the interval can be gradually increased, although never to longer than three months.

If lime deposits form, one ounce of Renacidin® (10 percent anhydrous citric acid, D-gluconic acid [as lactone]) is instilled into the bladder and held there for 30 minutes twice daily. The bladder then is thoroughly irrigated with a 1/16 to 1/64 solution of acetic acid in water to prevent subsequent calcium deposits on the catheter.

In most cases antiseptics are not necessary but if clinical manifestations or smear or culture examination indicates infection, chemical or antibiotic agents may be used to prevent the organisms from ascending to the kidneys.

A complication that sometimes occurs is that the catheter balloon will not deflate. Usually the cause

is that inadvertently a clamp has been placed across the balloon intake. Large balloons cannot simply be distended with water to the bursting point for there is not enough room to spare in the bladder. To remove the catheter in such circumstances, first instill one ounce of sterile oil and fill the bladder with water. Then injection of 5 ml of medical chloroform ether or acetone through the valve will cause the balloon to burst. The bladder then should be irrigated thoroughly and more oil instilled. The patient should be warned beforehand that a period of burning, pain, frequency and urgency of urination will follow. The extracted catheter must be inspected to make sure that all of the balloon is present. If not, whatever remains must be removed cystoscopically.

With 5 ml balloon catheters, injection of water until the bag bursts is proper. Pieces of rubber are more likely to be left behind with this method and at times cystoscopy is required. Catheter balloons will not burst on application of electrical current with an electrode. They must be punctured mechanically. If a urologist is not available, the bag can be deflated by first distending it with air, then aspirating through a suprapubic needle.

Occasionally catheters will have such great deposits of calcium that removal after balloon deflation seems impossible. Firm traction should be applied in such cases and the tube will come out, but pain and bleeding will result. The alternatives are cystoscopy or attempts at dissolving the calcium, if time permits.

Post-Catheter Care

After simple catheterization antiseptic agents should be given by mouth for five days to prevent infection. Usually indwelling catheters are in place for two to seven days or longer, and antiseptics should be given during that time as well as afterward.

After removal of the catheter the patient's ability to urinate must be ascertained. All the urine voided at each urination should be collected in separate bottles and the volume, time and color observed and recorded. For females, urine should be collected in a bed pan or commode and measured.

The patient must be questioned as to urgency, control, dysuria, size and force of the stream, ease or difficulty of urination and whether he feels relieved. If there is doubt, percussion of the suprapubic area will differentiate between the fullness of the bladder and symptoms referable to an irritable detrusor.

Effective antiseptic agents should be continued until the urine is free of pus and bacteria on methylene blue smear and it should be examined again two and six weeks after cessation of antiseptic treatment. If recrudescence occurs, the urine should be cultured and a suitable antiseptic agent given in the same sequence as was followed the first time. If relapse occurs again, urologic study is indicated. Careful attention to these details will prevent chronic infection. Cultures and disc sensitivity studies cannot be relied upon, as they are notoriously inaccurate.

CANCER FELLOWSHIPS

Postgraduate Fellowships in cancer for practicing physicians are available at the University of Southern California School of Medicine and the Los Angeles County-University of Southern California Medical Center. These Fellowships are sponsored by the National Cancer Institute, are of one month's duration and carry a stipend of \$750. Separate programs are available in tumor surgery, tumor pathology, radiation therapy, and medical oncology. Applicants should be Board eligible or Board certified and should submit a resumé of their professional background to Arthur J. Donovan, M.D., Program Director, Cancer Training Program, School of Medicine, University of Southern California, 2011 Zonal Avenue, Los Angeles, Ca. 90033.

CASE REPORTS

Larval Conjunctivitis in California Caused by *Oestrus Ovis*

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OCULAR MYIASIS, a disease uncommonly reported in California, has been well documented in the ophthalmic world literature.^{1,2} Two patients with acute conjunctivitis caused by the "sheep bot" larvae were recently treated at this center — a reminder that insect larvae should be included in the diagnostic consideration of cases of acute external ocular disease.

Scott³ of the U.S. Public Health Service analyzed the 111 cases of myiasis reported from the United States and Canada in the period 1952 to 1962, inclusive. Fifteen of these cases (16.7 percent) were ocular myiasis, of which 14 were caused by *Oestrus ovis* Linnaeus infestations and a single infestation probably by *Wohlfahrtia vigil* (Walker) a flesh fly (Sarcophagidae); both species are obligate parasites. The 15 cases of ocular myiasis were reported from ten states; three of

them were from California, apparently the only published record for the state.

The records of the Bureau of Vector Control, California State Department of Public Health, show four confirmed cases of ocular myiasis caused by first instar larvae of *O. ovis* in California, three of which were reported³ plus one additional case.* The times and places are as follows⁴: (1) Los Angeles (Westwood), Los Angeles County, 2 September 1952; (2) Avalon, Santa Catalina Island, Los Angeles County, 30 June 1960; (3) Bakersfield, Kern County, 3 June 1961 and (4) a hitherto unpublished record, Hanford, Kings County, 1 June 1962. The localities cited indicated the point from which the material was submitted, not necessarily the original point of infestation.

Reports of Cases

Case 1†. The evening of 6 July 1968 a 12-year-old Boy Scout reported to the camp health lodge on Santa Catalina Island, Los Angeles County, California, with complaint of left ocular irritation. He said that an hour and a half earlier a fly had landed momentarily in his left eye. At the time of the initial examination, a fiber-like foreign body was removed from the conjunctiva and a patch was placed over the eye. The following morning the patient returned to the health lodge complaining of continuing and increasing ocular irritation, and upon reexamination five insect larvae were removed from the left lower conjunctival cul-de-sac. The patient was carefully reexamined later the same day at the Jules Stein Eye Institute and only a mild conjunctival reaction was noted; no further symptoms nor sequelae occurred.

Case 2. A 24-year-old woman came to the emergency service at the UCLA Center for the Health Sciences complaining of irritation of the left eye. She said that at Avalon Bay, Santa Catalina Island, six hours previously, a pigeon that she was holding in her hands "spit in my eye." Soon

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Submitted 26 March 1969.

Reprint requests to: Department of Pathology, University of California, Los Angeles, School of Medicine, Los Angeles 90024 (Dr. Foos).

*Mr. Benjamin Keh supplied the information here reported on previously confirmed California cases.

†Details of initial treatment in this case were supplied by David E. Eifrig, M.D.



Figure 1.—First instar larva of *Oestrus ovis* (removed from conjunctiva in Case 2) showing buccal hooks (arrow) and prominences (with hooklets) on last abdominal segment.

after this incident, because of increasing irritation, she examined her eye and removed “about seven little bugs.” The ocular irritation, however, did not subside and upon her return to the mainland the patient saw two physicians who were apparently unable to find the cause of the worsening symptoms.

At the time of examination at the Jules Stein Eye Institute, the patient’s visual acuity in the right eye was normal while that in the affected left eye was 20/30+2. Two small, actively motile insect larvae were found by slit-lamp examination in the lower left conjunctival cul-de-sac and were removed uneventfully with swab sticks. There was no evidence of conjunctival laceration nor corneal abrasion, and except for the signs of mild conjunctivitis the remainder of the ocular examination was unremarkable. After removal of the larvae, the patient was quickly symptom-free and there was no recurrence of symptoms nor sequelae.

Entomological Aspects

The “sheep bot” *Oestrus ovis* Linnaeus (Diptera: Oestridae) is an obligate parasite, occasionally accidentally infesting man.

The normal hosts are sheep, goats, horses and other hoofed mammals, in which infestations by the parasitic larvae occur in the nasal region and the frontal or maxillary sinuses. *Oestrus ovis* occurs throughout the world wherever there are domestic or wild sheep and goats. In regions of the world where man is closely associated with sheep and goats, human infestations are common, usually resulting in ocular myiasis. However, nasal and oral myiasis by *O. ovis* may also occur.

Human infestation by *O. ovis* is the most common cause of ocular myiasis in the United States (14 of 15 confirmed cases from 1952 through 1962). Many cases, however, are overlooked, are not reported, or remain unconfirmed.

The adult fly is grayish-brown with dark spots on the dorsum of the thorax and abdomen, has a yellowish head and is about one-half inch long (10 to 12 mm). No feeding occurs during this stage; however, larvae are developed within the female and may be sprayed into the eyes, nose and throat of the host. As many as 50 first-stage larvae have been removed from the conjunctival sac of a single human patient.⁵ The white first instar larvae is elongate oval about 1 mm long, with two strong recurved buccal hooks, and two prominences on the last abdominal segment, which each have 10 or 11 “shark tooth shaped” hooklets (Figure 1).

Confirmation of ocular infestation by *O. ovis* was made at the laboratories of medical entomology in the Division of Infectious and Tropical Diseases, School of Public Health, University of California, Los Angeles. In this regard it should be emphasized that to document cases of myiasis it is necessary to preserve the specimens in 70-80 percent ethyl alcohol for subsequent identification by a specialist.

Discussion

The agent responsible for the conjunctival symptoms was in both cases documented as first stage larvae of the “sheep bot,” *Oestrus ovis*. In Case 1, living larvae were deposited on the conjunctival mucous membranes by the alighting female; in Case 2, larvae-deposition from flight was the probable mechanism.

The locale of the “sheep bot” infestation in these two cases, Santa Catalina Island, is recognized both by inhabitants of the island and public health agencies as an enzootic focus of *O. ovis*. There are approximately 15 cases of human ocular myiasis treated in Avalon each year.⁶ Most such cases are uncomplicated and do not come to the attention of mainland physicians. Thus, it is not surprising that in both cases in this report the cause of the ocular irritation escaped routine examination.

Although larval development is arrested in the accidental parasitism of man by *O. ovis*, until the larvae are removed from the conjunctiva, considerable morbidity can occur through mechanical and chemical irritation. If the presence of the

larvae is unrecognized, patients may be symptomatic for a protracted period. It is the intent of this report to reinforce the diagnostic awareness of larval conjunctivitis and to make note of the fact that simple therapeutic measures can reduce the associated morbidity.

Summary

Two cases of acute conjunctivitis caused by the infestation with the first stage larvae of the "sheep bot," *Oestrus ovis*, are reported. Also mentioned is another unpublished California case from the records of the Bureau of Vector Control. Al-

though an uncommon cause of ocular disease, the etiologic relationship of "sheep bot" strikes to larval conjunctivitis and the endemicity of this condition on Santa Catalina Island are reemphasized.

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PHLEBOTROMBOSIS — PLICATE OR LIGATE?

"The curative treatment for phlebotrombosis is vein ligation. Now there's a great deal of question about whether one should plicate or ligate. Surgeons who . . . want to plicate the vein . . . usually begin with a statement like this, 'Since the sequelae following vein ligation are so disabling, we think that a grid should be used or plication should be done.' Then they go on to describe a new method. The premise here is wrong. We've had more experience in inferior vena caval ligation than anyone else in the world; and that experience has shown us that if a patient has swelling before the cava is ligated, he will have persistent swelling afterward. If . . . a patient has no swelling beforehand (and he usually doesn't if he has phlebotrombosis)—and you tie the cava, wrap his extremities from his toes to his groin, and mobilize him immediately, he will not get edema. . . . I have no objection to using a grid or anything else—I think it's all right. But ligation is a lifesaving procedure. I think many times thrombectomy is indicated, particularly if there is any edema. But thrombectomy, unless it is done by a man who is trained in vascular surgery, is dangerous. Ligation of the cava is something any surgeon can do, and it's a lifesaving procedure."

—ALTON OCHSNER, M.D., New Orleans
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scription series of tape-recorded programs.

Congenital Histiocytosis X

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LETTERER-SIWE DISEASE is a generalized proliferation of histiocytes throughout all tissues that contain reticuloendothelial cells. It is the malignant end of a spectrum of so-called non-lipid reticuloendotheliosis, or histiocytosis x. It is characterized by rash, fever, anemia, hepatosplenomegaly and osteolytic bone lesions. It usually occurs in children under one year of age. Congenital Letterer-Siwe disease is extremely rare; including the case here reported, there are reports of 16 cases in the literature.¹⁻⁸

Report of a Case

The patient was a 7 pound, 7½ ounce white female infant born at term, 15 July 1967, at San Bernardino County General Hospital after an uneventful pregnancy terminated by precipitous delivery. No history of infectious disease or other prenatal problem could be elicited from the mother. At birth, a generalized, papular, crusting rash with lesions 0.5 to 1 cm in diameter covered the entire body (Figures 1 and 2). The liver was palpated 3 cm below the right costal margin. The rest of the physical examination was within normal limits. Leukocytes numbered 12,000 per cu mm of blood with 57 segmented neutrophils and one stab. The hemoglobin was 22 grams per 100 ml. The packed cell volume was 68 percent. A VDRL test was nonreactive. The patient was isolated, treated with soap (pHiso-Hex®) and water cleansings, application of an ointment containing polymyxin B, bacitracin and neomycin (Neosporin®), and administration of methicillin. Culture of a



Figure 1.—Generalized, crusting, papular rash photographed at three days of age.



Figure 2.—Detail of crusting lesions.

skin lesion was sterile. A skin punch biopsy specimen of a typical lesion at seven days of age, was reported as showing:

"A section of skin marked by slight hyperkeratosis and irregular parakeratosis with regular acanthosis of the epidermis. Numerous foci of large histiocytes and chronic inflammatory cells are seen in the papillary dermis but no disruption of the basement membrane or destruction of the dermal-epidermal junction is present. No sub-epidermal bullae are seen. Diagnosis: Chronic inflammation, non-specific. Special stain for mast cells is negative." (See Figure 3)

A Wright-stained smear of the skin lesions was negative. X-ray films of the skull and of the bones showed no abnormality. At 12 days of age, all previous therapy was stopped and a hydrophilic lotion was applied to the rash. The rash persisted, but the baby otherwise appeared to be doing well and gaining weight. At 27 days of age she was discharged from the hospital.

As an outpatient she was treated variously with hydrocortisone cream and an ointment containing a mixture of antibiotics (Mycolog®). At four

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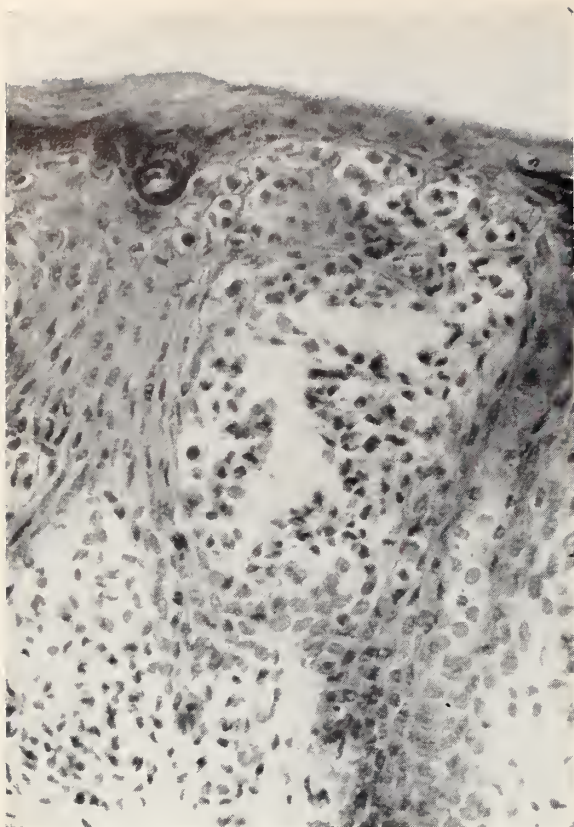


Figure 3.—Skin punch biopsy at seven days of age demonstrating large histiocytes filling dermal papilla.

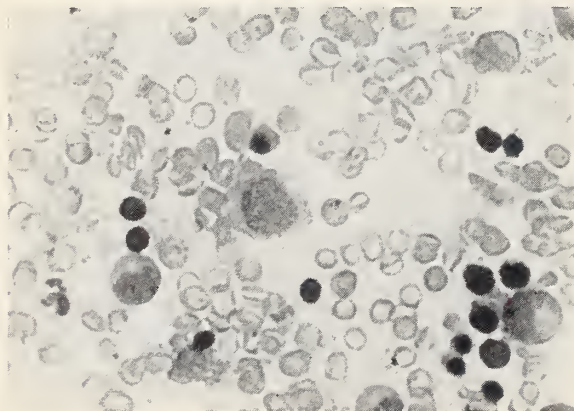


Figure 4.—Wright-stained smear of bone marrow, 400 X, showing reticulum cell (histiocyte) in center. Patient was 4½ months of age.

months of age, the patient was brought back to the hospital with fever, an upper respiratory tract infection, generalized lymphadenopathy and hepatomegaly. A roentgenogram of the chest showed diffuse nodular granular infiltrate. The hemoglobin was 11.1 grams per 100 ml. Leukocytes numbered 14,100 and platelets 200,000 per cu mm. A lytic lesion in the occipital bone was noted.



Figure 5.—Section of right inguinal lymph node revealing effacement of architecture. Patient was 4½ months of age. Hematoxylin and Eosin X 25.

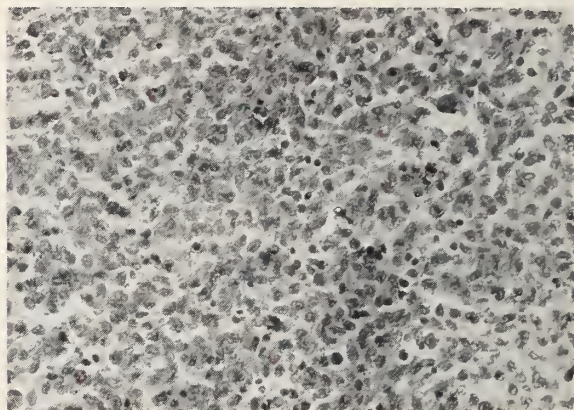


Figure 6.—Higher magnification of specimen in Figure 5 reveals diffuse proliferation of histiocytes. Mitoses are present.

A diagnosis of probable Letterer-Siwe disease was made. Bone marrow aspiration and right inguinal lymph node biopsy confirmed the diagnosis (Figures 4, 5, 6). Intravenous therapy with vincristine sulfate was begun 12 December 1967, at five months of age. Dosage was increased from 0.05 mg per kilogram of body weight per dose to 0.10 mg per dose over a three-week period. Blood transfusions were given. Intercurrent infections were treated with antibiotics. On 15 January 1968, at six months of age, prednisone, 10 mg four times daily, was begun. The lytic lesion of the skull was noted to have enlarged, but the clinical condition of the baby began to improve gradually and she was discharged 12 March 1968, at eight months of age. One platelet count was 50,000, but the remainder were well within normal limits. Prednisone, 10 mg four times daily, and vincristine sulfate, 0.25 mg intravenously at weekly intervals, were continued. On 25 March 1968 the patient

TABLE 1.—Data on Present Case and Five Cases Reported by Others

	Age at Diagnosis	Therapy	Result
Present Case	4 mo.	Vincristine Prednisone Antibiotics	Died 9 mo.
Hertz, Hambrick	2 days	Vincristine Prednisone	Alive and well 2 yr.
Jones, et al.	3½ mo.	Irradiation Hydrocortisone	Died 4½ mo.
	3½ mo.	Vinblastine Methotrexate Prednisone	Alive and well 29 mo.
	7 wk.	None	Alive and well 7 mo.
	Early infancy	None	Alive and well 1½ yr.

was readmitted to the hospital and treated for thrush and skin pustules with nystatin (Mycostatin®) and ampicillin. During this period, the treatment with prednisone and vincristine sulfate was continued. The patient had fever spikes over the next ten days. On 20 April 1968, chest roentgenogram revealed marked increase in the diffuse lung infiltrate; this was treated with high doses of ampicillin and kanamycin. On 21 April, at nine months of age, the patient died.

At autopsy involvement of the spleen and lungs was noted, but no involvement of the liver or lymph nodes. Apparent immediate cause of death was bronchopneumonia.

Discussion

In the past, Letterer-Siwe's disease has been considered to be always fatal. More recent reports indicate this is not true. Lahey⁹ reported a mortality rate of 70 percent when the disease occurred up to the age of six months. He concluded the younger the child, the worse the prognosis appeared to be.

Hertz and Hambrick⁶ recently published a case report of an infant with congenital Letterer-Siwe disease diagnosed by skin biopsy at 48 hours of age. This patient received prompt treatment with vincristine sulfate, 0.150 mg per kg of body weight per week, and prednisone, 5 mg per kg per day. The infant received prednisone therapy for six weeks and vincristine therapy for eight weeks. His course was relatively uncomplicated, but oral thrush developed and there was a patchy area of pulmonary consolidation at one point. Weight gain ceased during the course of therapy. The spleen increased in size on the third day of life, but after discontinuation of therapy the infant did well and is now two years of age and on physical examination appeared normal. (See Table 1.)

Jones, Welton and Gilbert⁷ published a report of three cases of congenital Letterer-Siwe disease. The first was in a 3½-month-old infant with a generalized crusted vesicular rash present since birth. A skin biopsy was considered diagnostic of Letterer-Siwe disease. He was treated with radiation to oral lesions and hydrocortisone, 15 mg, four times daily and died at 4½ months of age. Autopsy confirmed the diagnosis.

In the second case the patient was an infant admitted at 3½ months of age with a skin rash present since birth. A skin biopsy was interpreted as diagnostic of Letterer-Siwe disease. He was treated with vinblastine, 4 to 8 mg per square meter of body surface intravenously once a week for six weeks with dramatic regression of skin and gingival lesions. At eight months of age, there was a recurrence which responded to therapy with vinblastine. Recurrence occurred two months later and methotrexate, 15 mg per square meter intramuscularly twice a week, was continued for three months. The patient was readmitted at 13 months of age with bone marrow depression and evidence of recurrence.

He was maintained on prednisone, 20 mg every other day, until two years of age. He is currently receiving methotrexate therapy and at 29 months of age was asymptomatic except for increased nasopharyngeal mucus.

The patient in the third case had a rash which was noted on the first day of life. Skin biopsy was consistent with the diagnosis of Letterer-Siwe disease. No systemic symptoms developed other than the skin lesions, which eventually disappeared without therapy. This baby was last seen at seven months of age with no evidence of the disease.

A fourth patient of Jones¹⁰ had a similar rash in early infancy with similar skin biopsy studies. He was well at 1½ years of age after no treatment.

Etiology

The cause of Letterer-Siwe disease remains unknown. There have been reports of familial incidence of this disease,^{11,16} but in a report by Lightwood and Tizard,¹³ one of a set of monozygotic twins had Letterer-Siwe disease at six months of age, and the other had shown no evidence of the disease at any time up to the time of last report at age seven.

Letterer-Siwe disease has not been defined as a neoplasm, but the clinical course is usually malignant. Lahey¹⁷ found improvement in 85 percent of patients with histiocytosis X treated with vinblastine. His report suggested the sooner the therapy was begun, the better results would be.

The histologic features of Letterer-Siwe disease are very similar to those of reticulum cell sarcoma. Reticulum cell sarcoma has been found to frequently respond favorably to vincristine sulfate given in low doses over long periods.¹⁸ Thus a trial of vincristine sulfate in the therapy of Letterer-Siwe disease would seem justified.

Implications

In all but three of the reported cases of congenital Letterer-Siwe disease the patient presented with skin lesions only. Of the others, only one had no rash, and this was a stillborn. On this basis, tissue diagnosis with skin biopsy is usually advisable.

Early diagnosis by skin biopsy, read with a high degree of suspicion, combined with early and vigorous therapy might favorably alter the prognosis of this disease. An alternate postulate is that there is a cutaneous form of Letterer-Siwe disease which is sometimes self-limiting.

Summary

A case of congenital Letterer-Siwe disease is reported. The recent literature is reviewed. Diagnosis and therapy are discussed. It is suggested that early diagnosis and treatment might favorably alter the prognosis of this disease.

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Progress in Disseminated Intravascular Coagulation

Part II

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Pediatrics

Hyaline Membrane Disease

Hyaline membrane disease (idiopathic respiratory distress syndrome) is still one of the major problems in pediatrics. The demonstration by Hathaway and coworkers⁵² that this disease is accompanied by disseminated intravascular coagulation may represent a significant advance toward an ultimate solution of the pathogenesis of this condition. These investigators studied six infants with *severe* respiratory distress syndrome and found thrombocytopenia, prolonged bleeding time, hypocoagulability (as demonstrated by thromboelastography) and a decrease in Factors v and VIII. Fibrin split products were occasionally found in the serum. At autopsy these infants showed hyaline membranes and hemorrhages, and three had pulmonary vascular fibrin thrombi. In a larger group of infants with *mild* respiratory distress, all patients recovered and most had increased amounts of fibrin split products in their blood. This suggests that the clotting episode was proportional to the severity of the respiratory disease.

Although Hathaway was unable to alter the course of the disease with heparin, Parmentier (in Belgium) made an interesting observation.⁵³ Among 27 newborn infants who had received exsanguination-transfusion for iso-immunization,

only one had hyaline membrane disease. In a control group, the incidence was 33.7 percent. Parmentier noted that the infants who had the exchange transfusions were given 0.5 ml of heparin before the transfusion and suggested that this may have prevented or ameliorated the respiratory disease. It may be that the timing of heparin treatment is critical and that the infants reported upon by Parmentier were given heparin early enough to affect the disease.

In a recent report to the Eastern Section of the American Federation for Clinical Research, Huber⁵⁴ described the production of pulmonary hyaline membrane in dogs by continuous intravenous infusion of thrombin.

All these studies are in a preliminary stage. There is no doubt that disseminated intravascular coagulation is associated with hyaline membrane disease, but whether it is a cause or an effect of the disease remains to be shown.

Cyanotic Congenital Heart Disease

The occurrence of a hemorrhagic diathesis in certain patients with cyanotic congenital heart disease may constitute a serious complication. Bahnson and Ziegler⁵⁵ observed fatal massive bleeding in seven of ninety-nine patients following cardiac operations, and thrombosis in eight others. Hartmann⁵⁶ reviewed 31 cases and found significant thrombocytopenia and a decreased concentration of fibrinogen and prothrombin in patients with erythrocytosis. Paul et al⁵⁷ reported 200 cases of cyanotic heart disease and found significant thrombocytopenia in patients with hema-

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tocrits greater than 65 percent and oxygen saturation less than 70 percent.

Although surgical operation on the heart seems to be the major challenge to hemostasis in these patients, they may bleed spontaneously or from minor trauma as well. In this disease, the intravascular clotting is predominantly in the pulmonary circulation. Rich⁵⁸ described the pulmonary thrombi as extensive and involving small vessels with evidence of recurrent episodes of thrombosis. Occasionally, large vessel thrombosis in the cerebral vessels and aorta have been reported, but the major amount of clotting is in the lungs.

Several recent therapeutic trials with heparin and epsilon aminocaproic acid have brought considerable hope of a solution of this problem.

From the Walter Reed Hospital, Dennis et al⁵⁹ reported a patient with cyanotic congenital heart disease who responded to treatment with heparin.

The patient was a 10-month-old boy who was cyanotic and had a heart murmur at birth. He was a well developed infant but had clubbing of the fingers and toes. He was tachypneic, and had a systolic Grade II/VI murmur heard at the upper left sternal border with a split second pulmonic heart sound. X-ray films revealed increased density of the pulmonary vasculature and cardiomegaly. An electrocardiogram demonstrated right axis deviation with evidence of right atrial and biventricular hypertrophy.

On admission, the hematocrit was 85 percent and platelets numbered 17,000 per cu mm. The prothrombin time was 17 percent, and there were severe deficiencies of Factors v and VIII. The thrombin time was prolonged and fibrin split products were present in the plasma.

Heparin therapy was instituted with a dose of 1.0 to 1.5 mg/kg at 6-hour intervals to maintain a clotting time of 25 minutes. Within one week, there was a complete correction of the factors of the hemostatic mechanism.

A Blalock-Hanlon procedure was performed while the child was heparinized, and there were no hemorrhagic complications. Heparin was discontinued after operation, and this was accompanied by a transitory decrease in the levels of Factors v and VIII and an abnormal thrombin time. The patient made an uneventful recovery and was discharged from the hospital 10 days postoperatively.

Dennis et al⁶⁰ subsequently observed improvement in thrombocytopenia, prothrombin time,

partial thromboplastin time, thrombin time, Factors v and VIII levels, and disappearance of fibrin split products following heparin therapy in five cases of cyanotic congenital heart disease.

The studies of Brodsky et al⁶¹ suggest that in addition to disseminated intravascular coagulation, fibrinolysin activation may play an important role in the alteration of the hemostatic mechanism in these patients. They studied three patients with cyanotic and three with acyanotic congenital heart disease and found evidence of some degree of fibrinolytic activity in all. They treated their patients with epsilon aminocaproic acid, and a partial to complete recovery of the coagulation values ensued within a few days. They observed one patient who did not respond to heparin but did respond to epsilon aminocaproic acid.

This raises the possibility that in cyanotic congenital heart disease, some of the patients may have a so-called "primary" activation of the fibrinolytic enzyme system. If this is true, then it is obviously of great importance to determine whether or not a given patient has primarily intravascular clotting or primary fibrinolysin activation.

In our experience, fibrinolysin activation is usually a consequence of disseminated intravascular coagulation. There are few diseases in which, if a consumption coagulopathy is demonstrated clinically, fibrin thrombi cannot be found in the tissues. However, in some patients, the activation of fibrinolysin is concomitant with a triggering of the clotting mechanism and may become the major factor in altering the hemostatic mechanism. Looking to the future, it is clear that a careful evaluation of the hemostatic mechanism is a necessary part of the work-up of a patient with congenital cyanotic heart disease, with appropriate correction of the defect before surgical operation. Whether or not heparin or epsilon aminocaproic acid (or both) will prove to be the most beneficial therapy will await further clinical trials.

Hemolytic-uremic syndrome

In 1955 Gasser et al⁶² described a complex of clinical symptoms consisting of acquired hemolytic anemia, acute renal failure, hemorrhagic diathesis and cerebral symptoms which they called the hemolytic-uremic syndrome. This entity seems to be very similar to thrombohemolytic thrombocytopenic purpura. In the hemolytic-uremic syndrome, which occurs more frequently in infants than older children, the thrombi are predominantly

located in the renal glomerular capillaries, whereas in thrombohemolytic thrombocytopenic purpura the thrombi are ubiquitous.

In 152 cases of hemolytic-uremic syndrome recently reviewed by Piel and Phibbs⁶³ 61 deaths occurred. In 39 of 49 cases which came to autopsy, bilateral renal cortical necrosis (17 cases), thrombi of the glomerular capillaries, or both, were demonstrated. Five cases showed widespread microthrombosis of the vessels in many organs of the body. These observers also reviewed 23 cases of thrombohemolytic thrombocytopenic purpura in childhood. In 8 of 22 autopsy cases, thrombi were found only in the kidney.

Reports of Treated Cases. Various therapeutic agents have been applied, including exchange transfusions, dialysis, steroids and anticoagulants. Treatment with heparin was used in several cases to halt the process of subacute intravascular coagulation.

Piel and Phibbs reported two cases treated with heparin for 9 to 11 days, respectively, early in the disease. In both cases the platelets rose 48 hours after onset of heparinization. Additional therapy consisted of peritoneal dialysis because of the extended period of anuria (6 to 9 days). The patients recovered and were discharged in good health.

Hitzig⁶⁴ reported three patients with the hemolytic-uremic syndrome treated with heparin over a longer period. The first patient, a 7-week-old boy, was treated with 2,500 to 5,000 units of heparin per day over a 12-day period, with fibrinogen (0.5 gram per day for the first three days), whole blood and a single dose of prednisolone. Diuresis occurred, hemolysis ceased and the platelets increased from 20,000 to 630,000 per cu mm three weeks after the treatment began. The second patient, a 4-year-old boy, was treated with heparin alone (no corticosteroid, no fibrinogen, or blood transfusion). In this patient, untreated for the first three days after onset of the disease, complete anuria, uremia and hemolytic anemia developed. Heparin therapy (2,500 units per day for 12 days) completely halted the progress of the illness. Laboratory measurements became normal after several weeks. In the third case, that of an 8-month-old boy, heparin was given for about four weeks (5,000 units a day). Additional therapy consisted of one blood transfusion and prednisolone (30 mg a day for about four weeks). In spite of the initial improvement of diuresis the

patient died about four weeks after the beginning of therapy.

Corticosteroids are reported to be of no benefit in the hemolytic-uremic syndrome.⁶⁵ On the contrary, they predispose animals to disseminated intravascular coagulation.

In 1964, Künzer and Aalam⁶⁶ described a case in which two episodes of the disease occurred in a period of two years. During the first episode an exchange transfusion was performed to overcome the anuria. The patient was free of symptoms for two years. In the second occurrence of the syndrome, heparin (40,000 units daily for eight days) was given after there was no clinical or hematologic response to prednisone. The patient recovered rapidly. The platelets rose in 15 hours from 8,000 to 260,000 per cu mm. No further bleeding occurred.

The cause of the hemolytic-uremic syndrome is as yet unknown, but there is some suggestion that viral infections may be the cause of the disease (Gianantonio et al,⁶⁵ Glasgow and Balduzzi⁶⁷). About 60 percent of 160 reported patients survived with treatment by conservative management, exchange transfusion, hemodialysis or steroids. The already reviewed cases in which patients were successfully treated with heparin were impressive for the good hematologic response to the anticoagulant. Because the *fatal* course of the hemolytic-uremic syndrome is caused by systemic intravascular coagulation with thrombotic occlusion of the renal glomerular capillaries, therapy with complete heparinization early in the disease has been used with apparent success.

Surgery

Somatic trauma is undoubtedly one of the most frequent causes of disseminated intravascular coagulation. Although no statistics are available, the frequency of traffic accidents and deaths by themselves are indicative of a high incidence. The clotting episode may be caused directly by the trauma or may be indirectly caused by secondary complications or even by therapeutic agents used in the management of emergency cases. In any specific case, or in any specific disease process, the occurrence of disseminated intravascular coagulation may play little or no role in morbidity or mortality, but in other disease processes it may be the major pathogenetic mechanism leading to serious secondary disease problems or to death.

The occurrence of disseminated intravascular coagulation following trauma has been well documented. Bergentz and Nilsson⁶⁸ studied the blood coagulation system after bilateral fractures of the femoral diaphyses of dogs. The animals were observed over a 30-hour period. A slight shortening of the coagulation time occurred during the first eight hours of the experiment. The platelet count decreased progressively after the trauma to reach a level of about 50 percent of the initial value at the end of the experiment. No significant changes in the levels of prothrombin and Factor VII were observed during the first 12 hours, but, after 24 and 30 hours, the values showed a decrease to about 50 percent of the original. Factor V decreased throughout the experimental period, but particularly during the first few hours after trauma. Factor VIII (antihemophilic globulin) decreased slightly during the first eight hours. Plasma fibrinogen decreased during the first eight hours in all dogs, and the decrease was most pronounced two hours after the fracture. The fibrinogen decreased from an average of 0.36 to 0.33 gm per 100 ml. A variety of tests revealed increased fibrinolytic activity during the first few hours after the trauma. The euglobulin clot lysis time decreased from a mean value of 225 minutes to 85 minutes within two hours. It then increased and at the end of 30 hours was much longer than before the experiment. The activity of the re-suspended plasma euglobulin precipitate on unheated bovine fibrin plates also increased during the first few hours. After 12 hours their activity also decreased to less than that found in the blood prior to trauma. The serum inhibitors of plasminogen activation by urokinase had a tendency to decrease during the first four hours, only to be followed by a marked increase at the end of the period, when the inhibitory activity was 179 percent of the pre-experimental value.

Another type of trauma was used in the experiments of Borgstrom et al⁶⁹ on rabbits. Contusion of the muscles of one thigh was used as standard trauma. The animals were anesthetized with pentobarbital (Nembutal®), both femoral veins were ligated and the muscles were contused by light blows with a padded hammer, the severity of the trauma being graded by variation of the number

of blows. The ligated veins were examined for thrombi 6 to 7 days after trauma.

In the control group with mere ligation of the femoral veins, only 1 out of 20 revealed a thrombus. In the groups with contusion of one hind limb by 50, 100, 150, and 200 blows, there were found 5, 14, 17, and 19 thrombi, respectively. The same number of thrombi was found on non-contused as on contused sides. The thrombi varied in length from a few millimeters to 1 to 2 centimeters and were always located below the ligature. Thrombi always formed first on the contused side, but later the same number was formed on the non-contused side.

The generalized nature of the effect of trauma was demonstrated by observations on the capillary vessels of the bulbar conjunctiva. Red blood cell aggregates appeared 1 to 3 hours after contusion, and aggregates were seen in arterioles, capillaries and venules. The flow became slower, and aggregates occluded parts of the capillary bed.

Following tissue injury, a reduction of the suspension-stability of the blood always occurs and leads to changes in the flow of blood with intravascular aggregation and erythrocytosis in capillary vessels. A reduction in the suspension stability of the blood can be caused by changes in the plasma proteins with increase of large and viscidizing molecules as noted by Fahraeus.⁷⁰ Cuthbertson⁷¹ showed that such changes occur after trauma, with decrease of albumin, and with increase of globulins, especially fibrinogen. Knisely et al⁷² found that the erythrocyte aggregation first appeared locally in a traumatized region and then became generalized if injury was severe enough. The administration of heparin during the early phase prevented both intravascular aggregation and thrombus formation. Erythrocyte aggregation and thrombus formation are parallel phenomena.

In man, Blaisdell, Aggeler et al⁷³ demonstrated that disseminated intravascular coagulation follows trauma. They found a consistent post-traumatic decrease in Factors II, V, VII, VIII, X and in platelets and plasminogen. Fibrinogen varied greatly and was increased, decreased or unchanged. Fibrin degradation products were often elevated but not consistently. Those patients who manifested severe intravascular coagulation of the type that was easily documented by changes in the clotting factors, rarely survived.

Causes of Intravascular Coagulation in Trauma

Although they are closely related, these mechanisms can be divided into *local*, and *systemic* for purposes of discussion.

Local

Severance of vessels of the microcirculation. Whenever small vessels, arterioles, capillaries or venules are cut across, thrombi composed of platelets and fibrin are quickly formed to seal off the end of the vessel. This is due in large part to the exposure of the blood to collagen or vascular basement membrane, which leads to platelet aggregation and eventual fibrin formation. The extent to which clotting occurs and to which coagulation factors are lowered in the circulating blood will obviously depend upon the extent of trauma, that is, the number of vessels cut across.

Release of tissue thromboplastin into the circulation. All tissues contain a phospholipid substance which is capable of triggering the clotting mechanism rapidly. The relative concentration of this material in cells varies from tissue to tissue. Tissue thromboplastin can be considered to have a beneficial effect in the occurrence of trauma because it hastens the clotting of shed blood and may aid in closing off vessels by thrombosis. If, however, the circumstance occurs that fragments of tissue or extracts of tissue gain entrance to the circulating blood, the effect may be deleterious, even lethal. These effects have been amply demonstrated experimentally by intravenous injection of tissue thromboplastin (Schneider⁷⁴ and Vasalli et al¹²).

That tissue or tissue extracts do get into the circulating blood in some traumatized patients is best illustrated by the observation of bone marrow embolism to the lung in patients with fractures. I have observed this phenomenon in older patients subjected to external cardiac massage in whom the fracture of sternum or manubrium was the source of bone marrow. Undoubtedly, it occurs in more extensive damage to bone or may occur in traumatic accidents.

Another clear evidence that tissue may gain access to the circulating blood in traumatized patients is the occurrence of fat embolism. Large fat droplets or fat cells are found in the pulmonary circulation at autopsy. The fact that these patients often exhibit evidence of disseminated intravascu-

lar coagulation has been largely overlooked. However, microthrombi composed of fibrin and platelets are found in the lungs of these patients. It seems quite likely that the tissue thromboplastin which gains access to the blood stream at the same time as the fat is more likely to be the lethal factor in these cases than the fat itself. Nevertheless, the presence of fat in the circulation is clear evidence that tissue and tissue extracts do get into the circulation following trauma.

The question of how frequently and how much tissue thromboplastin gets into the blood stream remains to be answered. In view of the variability of tissue thromboplastin concentration from one organ to the next, it will depend to a certain extent upon the organ or organs involved in the trauma. Also to a certain extent it will depend on the accident of cutting across vessels of a size large enough to allow entry of fragments of tissue, and it obviously requires the presence of an established or reestablished circulation in the incised part.

Ischemia. Ischemia implies a cessation of flow through a vascular bed, and it must be acknowledged that such an event is accompanied not only by deprivation of oxygen, but with acidosis, increased carbon dioxide and possibly changes in electrical potential, all of which may play a role in triggering clotting.

An example of this mechanism is found in the "crush syndrome." Crushing injury results in aggregation of platelets in the microcirculation of the crushed area.^{75,76}

Ischemia followed by recirculation of blood. If the vascular supply to an organ is cut off, the local thrombosis which follows will result in infarction of the tissue with very little systemic damage. If, however, the circulation is temporarily stopped and then subsequently reestablished, the result may be fatal.

The occurrence of local clotting after temporary ischemia was first demonstrated by Sheehan and Davis.⁷⁷ They clamped off the renal artery for a period of two hours and then released the clamp. Immediately after release of the clamp, blood circulated in the kidney but soon the flow stopped completely. They referred to this phenomenon as a "failed reflow." The secondary cessation of the circulation was due to the development of thrombi in the microcirculation.

The occurrence of disseminated clotting after temporary ischemia was first recognized in rela-

tion to intussusception of the intestinal tract.¹ The intussuscepted segment drags in with it portions of mesenteric veins and arteries. The length of the segment determines the extent of vascular involvement. With the slowing or cessation of blood flow in this variable portion of the vascular system, ischemic damage to the coagulation mechanism and the vessel wall occur. When the intussusception is reduced, blood may recirculate through this segment, and clumped platelets and procoagulant substances are swept into the general circulation. This induces intravascular clotting in distant organs.

Recently this phenomenon has been extensively explored by Blaisdell and Lim.⁷⁸ They encountered it first in patients undergoing major vascular operations, particularly operations for repair of ruptured aneurysm. In their search for the cause of death in these patients who had had an otherwise successful operation, they found thrombosis of the pulmonary microcirculation.

In attempts to elucidate the course of events, they reproduced the syndrome in dogs.^{79,80} This they did by the production of regional ischemia in the lower half of the body by temporary occlusion of the aorta below the renal arteries and simultaneous ligation of the collateral arterial flow. After four hours the aortic clamp was released and blood allowed to recirculate. Although no serious systemic problems were noted during the period of occlusion, shortly after release of the clamps respiratory distress developed and the animals eventually died. At autopsy most of the capillaries contained numerous masses of aggregated platelets and arterioles contained fibrin thrombi. As time progressed the lungs showed increasingly severe damage with atelectasis, edema, vascular congestion, and focal hemorrhage. The degree of morbidity and mortality was related to the duration of ischemia of the lower extremities and was proportional to the number of micro-emboli in the pulmonary circulation.

The etiologic role of the thrombi was clearly demonstrated when they prevented the lethal effect by heparinizing the animals before release of the clamp.

More recent studies⁸¹ have indicated the precise chain of events. They prepared a group of animals with a portocaval shunt which diverted the blood from the extremities through the liver. They subjected these dogs to the aortic clamping experiment and all the animals survived, with the ma-

jority of platelet masses in the liver rather than the lung. These experiments suggest that the platelet (and fibrin) thrombi are formed in the ischemic limbs during the period of aortic clamping, and with reestablishment of blood flow are then swept into the pulmonary circulation where they lodge and exert a profoundly deleterious effect on the blood pressure and the normal functioning of the lung, leading to death.

The repair of major vessels, sometimes necessitating temporary occlusion of the vessel, is fraught with this danger, in human patients as well as in experimental animals.

Systemic Factors

Anoxemia, cardiac arrest. The total cessation of the circulation associated with cardiac arrest results in intravascular coagulation. It represents the systemic example of local anoxia. Crowell⁸² was the first to demonstrate this when he induced cardiac arrest in dogs for a period of three minutes followed by reestablishment of the circulation. At autopsy, small blood clots were demonstrated in the pulmonary vessels. It was then shown that the survival rate of the dogs could be approximately doubled if the animals were heparinized.

Coon and Hodgson⁸³ have described the same phenomenon in patients suffering from cardiac arrest.

Shock. One of the most consistent sequelae to trauma is shock. Shock is a trigger to disseminated intravascular coagulation. This was first demonstrated by Crowell⁸⁴ in animals subjected to hemorrhagic shock. He produced a controlled steady state of shock (lowering the blood pressure to 50 mm of mercury for 90 minutes and 30 mm for 45 minutes) by bleeding the dogs into a reservoir containing citrate as the anticoagulant. A pronounced shortening of the whole blood coagulation time was found during the period of shock. When the animals' own blood was reinjected into the circulation, the blood pressure tended to rise to normal levels; but subsequently it dropped and after several hours the dogs died. Small blood clots were demonstrated in the pulmonary vessels by washing them out by reverse perfusion. Crowell was able to prevent death in nearly all dogs under the same experimental conditions if heparin was administered before shock developed.

In man, the occurrence of disseminated intravascular coagulation in shock has been amply documented by Hardaway.⁸⁵

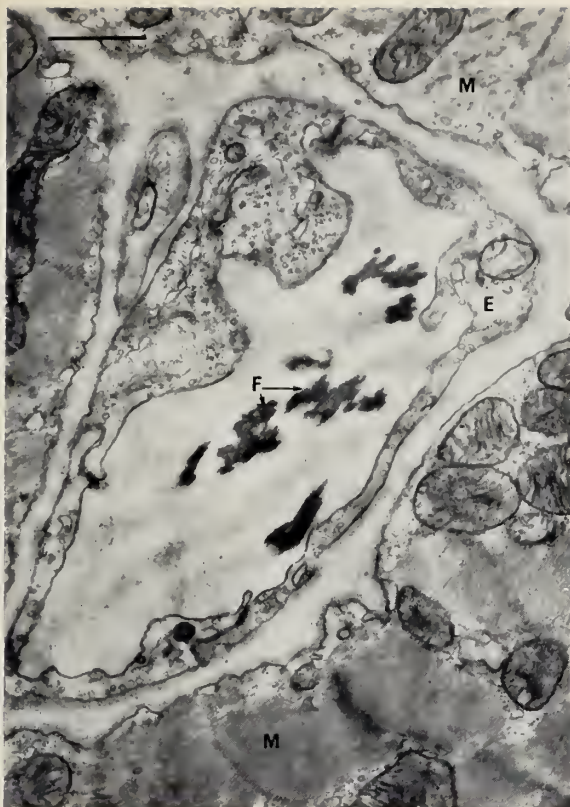


Figure 7.—Catecholamine shock. Monkey heart. Fibrin strands apparently floating free in the plasma of a myocardial capillary. $\times 21,600$. F=Fibrin. E=Endothelium. M=Cardiac muscle cell.

Bacterial endotoxin. Infections such as peritonitis, local abscesses and bronchopneumonia are frequent complications of trauma. They may be the source of a bacteremia which, due to release of bacterial endotoxin into the circulation, triggers intravascular clotting.

Endotoxin shock illustrates an important principle, namely, that considerable intravascular clotting may occur and not be visible by light microscopy. In animal experiments, large doses of bacterial endotoxin are lethal. Pathologic examination by the light microscope reveals congested vessels in many organs but no thrombi. However, electron microscopy in these animals readily reveals platelet clumps in capillaries of the lung and liver and fibrin strands in capillaries of all organs.⁸⁶ With the exception of the liver no occlusive thrombi are formed. Rather, the fibrin strands appear to be floating free in the plasma. Hematologic studies simultaneously show a drop in platelets and fibrinogen. This phenomenon is probably ascribable to a rapid massive activation of the fibrinolytic enzyme system which destroys the

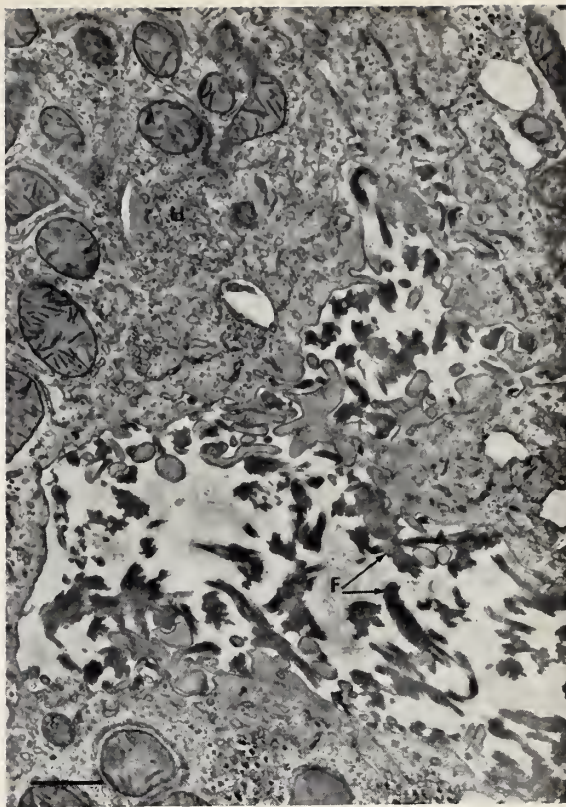


Figure 8.—Catecholamine shock. Monkey liver. Fibrin strands adherent to the microvilli lining the sinusoidal space. $\times 16,000$. F=Fibrin. H=Hepatic cell.

fibrin as fast as it is formed. This accounts for the frequent occurrence of disseminated intravascular coagulation, demonstrated by hematologic means, but not demonstrated by the routine light microscope examination.

Catecholamine shock. One of the common denominators in shock due to various causes is the release from the adrenal glands of high concentrations of epinephrine and norepinephrine. Whitaker and McKay recently studied the effect of high doses of epinephrine on the microcirculation and the coagulation mechanism.⁸⁷ Electron microscopy revealed strands of fibrin, associated with platelets, in capillaries or arterioles of the heart, spleen, liver, adrenal, kidney and placenta (Figures 7 and 8), and by hemostatic studies which showed reductions of platelets, fibrinogen and elevation of cryofibrinogen. Preheparinization prevented the reduction of fibrinogen and elevation of cryofibrinogen caused by epinephrine.

The survival time, when animals were infused continuously with epinephrine, was lengthened by anticoagulation with heparin, and shortened by

the addition of epsilon aminocaproic acid to inhibit fibrinolysis, showing that disseminated intravascular coagulation is a contributory lethal factor when animals are subjected to severe adrenergic stimulation.

The severity of the hemostatic response to epinephrine infusion paralleled the vascular response, and did not occur when the alpha-adrenergic receptor sites were blocked by phenoxybenzamine (Dibenzylamine®). The action of epinephrine is indirect and is mediated by the effect on the vascular system.

It seems quite likely that the release of vaso-motor active substances in shock in man may play a role in triggering the clotting.

Shock Due to Intravascular Clotting

The induction of disseminated intravascular coagulation by shock may become a two-edged sword, since disseminated intravascular clotting also causes hypotension. The infusion of thrombin into monkeys and rabbits causes an immediate but transient drop in blood pressure, which is prevented by heparinization beforehand.⁸⁸ Within certain limits the drop in blood pressure is directly proportional to the amount of thrombin given, and there is a direct relationship between the decrease in blood pressure and the decrease in circulating platelets and fibrinogen.

The superimposition of a clotting episode in an animal with shock due to another cause increases the lethality. In normal rabbits the LD₅₀ dose of thrombin was 24 units per kilogram. In animals subjected to catecholamine shock, the LD₅₀ was 11 units per kilogram. This suggests that hypotension due to other causes increases the hypotensive and lethal effect of disseminated intravascular coagulation.

Thromboembolic Disease

Thromboembolism remains a major complication of patients subjected to trauma. The experiments of Bergentz⁶⁸ demonstrated that trauma at distant sites may result in large vein thrombi under the conditions of local distortion of the vein, as in ligation. In a sense the trauma initiates an increased coagulability of the blood which then results in a thrombus at a distant site where circulatory dynamics are altered. Disseminated intravascular coagulation may thus lead to local large vein thrombosis.

Conversely, the release of a venous thrombus to the pulmonary circulation may lead to disseminated intravascular clotting. We have observed two patients with large pulmonary emboli with clear-cut histologic evidence of disseminated clotting.⁸⁹ Merskey and Johnson⁹⁰ have provided the hematologic evidence. They observed three patients with depletion of the circulating clotting factors, thrombocytopenia and fibrinolysin activation following pulmonary embolism. Schoenfeld et al⁹¹ showed an increase in acid phosphatase in the serum of two patients with pulmonary emboli. Acid phosphatase rises when platelets are destroyed in large numbers *in vivo*. A more direct demonstration of platelet damage following pulmonary embolism comes from the studies of Hirsh and McBride,⁹² who found increased platelet adhesiveness in patients with pulmonary embolism. Platelet adhesiveness is increased in disseminated intravascular coagulation.

The clinical use of heparin has provided further evidence. Thomas⁹³ pointed out that the use of heparin greatly diminishes the mortality following pulmonary embolism. This observation also indicates that the clotting episode in some patients is the lethal factor.

The major question remaining is the mechanism by which pulmonary embolism triggers the clotting mechanism. It may be that it is initiated by release of thrombin absorbed onto the fibrin of the thrombus, or contained within pockets of serum within the clot, at the time of impaction of the embolus against the walls of the pulmonary artery. Anoxia, endothelial damage, and release of serotonin and histamine from damaged platelets may be contributory factors.

Iatrogenic Factors

A number of accidents may occur in the therapy of a traumatized patient which in themselves may lead to intravascular coagulation. Hemolytic transfusion reactions, multiple transfusions, and blood contaminated with Gram-negative bacteria have been shown to cause disseminated intravascular clotting.¹ The injection of therapeutic agents intravenously, particularly colloidal substances, may occasionally be responsible. Intravascular coagulation may develop in an occasional patient subjected to extracorporeal circulation.

In the analysis of any patient who presents pathologic, hematologic or clinical evidence of disseminated intravascular coagulation all these

possibilities must be kept in mind in order to determine the precise cause or causes of the clotting episode.

Kidney Transplants

Every group with experience in clinical renal transplantation has experienced a number of catastrophic failures, commonly referred to as "hyperacute" rejections, during the first minutes to hours after transplantation. In some cases, the homograft was irreparably injured in this way even while the patient was still on the operating table.

Starzl¹⁹⁴ reported such hyperacute rejection five times in three human recipients. The kidneys, removed 1 to 54 days later, had cortical necrosis. The major vessels were patent, but the arterioles and glomeruli were the site of fibrin deposition. The findings were characteristic of the generalized Shwartzman reaction.

In a search for the cause of intravascular clotting in these kidneys, efforts were made to determine whether or not the patients had had a Gram-negative endotoxemia. Cultures of the dialysate baths were reviewed for the period during which three patients were treated on the artificial kidney. Growth of Gram-negative organisms was invariably present, the most common bacteria being *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, *Escherichia coli* and paracolon strains. Nevertheless, no bacteria were found in available blood specimens and a search for endotoxin in the blood yielded negative results.

Hemolysis, increased coagulability of the blood caused by the artificial kidney, and the blockade of the reticuloendothelial system by immunosuppressive drugs, were considered as possible causal factors.

While any or all of these factors may have contributed to the clotting episode, the studies of Williams et al⁹⁵ point to a more likely mechanism. These investigators described studies in severe cases of "hyperacute" rejection. They observed a significant accumulation of "hyperacute" rejections in recipients of multiple grafts and inferred that immunologic mechanisms operated in these rejections. The almost immediate occurrence of the reaction, as well as the absence of mononuclear-cell infiltration in the grafts, argued against the involvement of cell-mediated immunity in these rejections. They suggested that the rejection may be related to humoral antibodies. This relation was suggested by one of their patients who

was demonstrated to have an ABO incompatibility. The patient was a Group O recipient who received a graft from a Group B donor and the anti-B humoral antibodies were implicated. Other observers have also reported acute anuria of grafts mismatched for ABO groups.

In other cases reported by Williams and co-workers, antibodies to tissue isoantigens were demonstrated by means of mixed agglutination and lymphocytotoxicity tests in pre-transplantation sera. The lymphocytotoxicity test provided evidence for the presence of antibodies specifically combining with the donor antigens in two of six cases. However, the mixed agglutination tests provided such evidence in all but one case, either by directly demonstrating antibodies acting upon the donor's cell culture or by demonstrating that antibodies were bound to the grafted tissue. Moreover, in two patients, the disappearance of antibodies from the circulation was observed after the renal graft, and this could clearly be related to the removal of antibodies by the graft.

The findings imply that this form of rejection may result from the effect of humoral antibodies on the graft.

Our own interpretation would be that the deposition of circulating antibody on the endothelium of arteries and capillaries of the donor kidney would result in a layer of antigen-antibody complex on the endothelial surface. The ability of antigen-antibody complex to trigger the clotting mechanism has been well documented.¹ This would explain also the localization of thrombi in the renal circulation and the lack of evidence of clotting in other organs of the body in these cases.

It is possible that anticoagulant therapy might be useful in these cases, if given in time, but a better solution would be to attempt to avoid the immunologic incompatibility through appropriate antibody tests.

Obstetrics

Postpartum Hemolytic-Uremic Syndrome. This condition is fortunately a rare one, but it is a serious problem that occasionally must be faced by both obstetrician and internist. It has been described under a variety of labels, including *postpartum malignant nephrosclerosis*, *postpartum renal failure*, and *postpartum malignant hypertension*. It has been included in series of patients with the diagnosis of thrombotic thrombocytopenic purpura and undoubtedly many of these

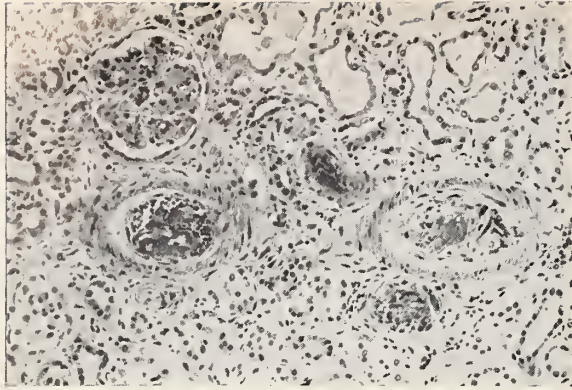


Figure 9.—Postpartum hemolytic-uremic syndrome. Kidney. Old and recent thrombi obstruct the lumen of a small artery. Hematoxylin and eosin stain. $\times 160$.

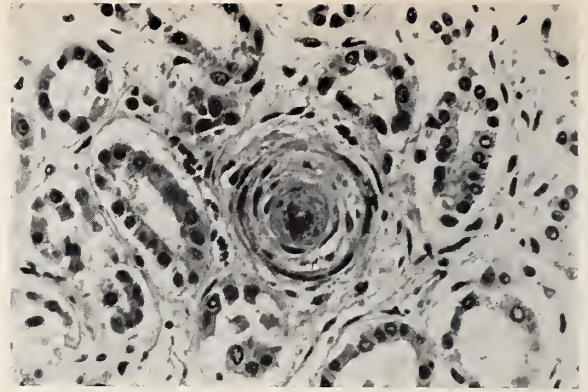


Figure 10.—Postpartum hemolytic-uremic syndrome. Kidney. Hyperplastic thickening of arteriolar wall. Hematoxylin and eosin stain. $\times 400$.

patients in the past have been included in series of patients categorized as postpartum toxemia of pregnancy.

We agree with Clarkson⁹⁶ that until the cause of the disease is found, the best name for it is *postpartum hemolytic-uremic syndrome*. The name carries with it the implication of a fundamental component of the disease—that is, disseminated intravascular coagulation—and it is descriptive of two of the major clinical manifestations of the disease. Also, to a large extent, it is quite similar to the hemolytic-uremic syndrome of infants.

Clinically, the disease is characterized by a normal prepartum and intrapartum course without evidence of hypertension, renal disease or toxemia. Soon after delivery (three days to ten weeks) a prodrome of mild gastrointestinal disturbance, fever and upper respiratory symptoms appears. Some patients present initially with anemia, edema, and a hemorrhagic diathesis with purpura, bleeding or bruising and ecchymoses without preceding minor complaints. Acute renal failure always develops. Although none of the patients thus far observed were hypertensive before the illness, the blood pressure became elevated during the disease in half of the cases. The anemia is characterized by a negative Coombs test and the appearance in the smear of “burr” cells, fragmented cells, microspherocytes and “helmet” cells, which is characteristic of “micro-angiopathic hemolysis.”

Tissue examination has proved that these patients have undergone an episode, or perhaps repeated episodes, of disseminated intravascular coagulation. Although the kidneys bear the brunt of the clotting process, fibrin deposits have been found in many organs. Three cases have exhibited

verrucous (non-bacterial thrombotic) endocarditis which we have shown to be a complication of disseminated intravascular coagulation. Focal hepatic necrosis, pulmonary thrombi and focal hemorrhage, microscopic infarction and hemorrhage in the brain are indicative of the disseminated nature of the clotting.

But the kidneys demonstrate it best. In my experience these cases are unique, from the standpoint of the pathologic changes, and present certain differences that may serve to distinguish the process from either the hemolytic-uremic syndrome of infants or thrombotic thrombocytopenic purpura.

The most striking abnormality is the presence of organized recanalized thrombi in the arcuate and straight arteries to the cortex. The walls of these vessels are perfectly normal with no damage to the smooth muscle cells, but the lumina are practically obliterated by a fibrous proliferation with a tiny recanalized lumen that can only be explained as an organized thrombus. Occasional fresh fibrin thrombi are found in these vessels, sometimes associated with focal infarction, indicating that this is a recurrent process, but for the most part the thrombi are old (Figure 9). In addition, the precapillary arterioles show the concentric laminated proliferation of smooth muscle cells that we ordinarily associate with malignant hypertension (Figure 10). This in spite of the fact that the hypertension is usually mild or may even be absent.

The glomeruli are involved in a variety of ways. A few show recent glomerular capillary thrombi, with hemorrhage into the capsular space. Many are atrophic and shrunken, leaving a very dis-

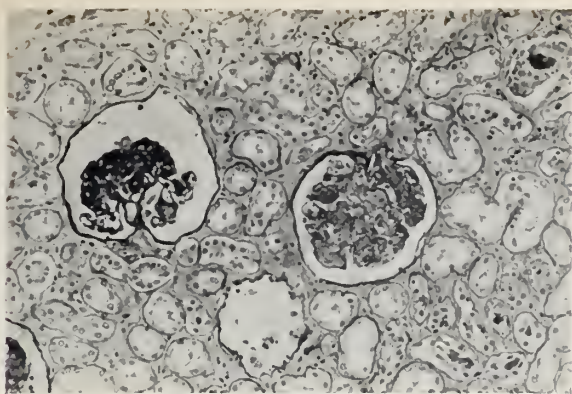


Figure 11.— Postpartum hemolytic-uremic syndrome. Kidney. Atrophic glomeruli. Periodic Acid Schiff reaction. $\times 160$.

tended, almost cystic, capsular space (Figure 11). These latter imply long-standing ischemia to these glomeruli. Still other glomeruli show a complete hyalinization and obliteration of the capillary tuft with a covering of enlarged epithelial cells of the visceral layer of Bowman's capsule.

This combination of changes seems to me unique, but the greatest overlap occurs with the hemolytic-uremic syndrome of infants. The renal lesions of thrombotic thrombocytopenic purpura are characterized by platelet and fibrin thrombi in the hilar region of the glomerulus or by organized recanalized thrombi in the efferent arteriole. As a corollary, thrombotic thrombocytopenic purpura is seldom associated with renal insufficiency.

Thus far, anticoagulant therapy with heparin, which has been tried in a few of these patients, has not been of any benefit.⁹⁶ Most have died of renal failure. However, these patients have usually been treated long after the initial clotting episode, and it is unlikely that anticoagulants will be of any help unless the disease is diagnosed in its early stages.

Conclusions

Disseminated intravascular coagulation is an important intermediary mechanism of disease. It is a dynamic biologic response involving many inextricably interrelated chemical substances and physiological responses. It is triggered by eight basic etiologic agents including: (1) intravascular hemolysis, (2) tissue thromboplastin, (3) bacterial endotoxin, (4) proteolytic enzymes, (5) particulate or colloidal matter, (6) anoxia and anoxemia, (7) endothelial damage, and (8) ingestion of certain lipid substances.

Disseminated intravascular clotting often pre-

sents a characteristic constellation of clinical signs and symptoms. These include hypotension (shock), a bleeding tendency, oliguria or anuria, convulsions and coma, nausea and vomiting, diarrhea, abdominal pain, back pain, dyspnea, and cyanosis. Not all are present in every case.

A clinical test for disseminated intravascular coagulation has been proposed, consisting of a therapeutic trial of heparin with an evaluation of the response (or lack of it) of the hemostatic mechanism.

In a few specific disease entities, heparin therapy has proved effective. These include acute renal failure in glomerulonephritis, cyanotic congenital heart disease, infantile hemolytic-uremic syndrome, a few selected cases of cirrhosis of the liver and a strong suggestion of benefit in hyaline membrane disease (respiratory distress syndrome).

Some specific diseases have not responded to heparin — for example, postpartum hemolytic-uremic syndrome. It is possible that heparinization was begun too late and might be useful if given early in the disease.

It is not to be expected that heparin will prove to be a panacea. Further trials with anticoagulants are indicated in order to determine the actual usefulness of heparin in many disease states.

For the future, it is possible that agents not ordinarily considered anticoagulant may prove extremely useful. The indirect antithrombotic effect of alpha-adrenergic blockade by phenoxybenzamine is one of these. The inhibition of platelet aggregation by anti-inflammatory drugs such as sodium salicylate, sulfinpyrazone and phenylbutazone must be tried in these diseases.

Disseminated intravascular coagulation is the major pathogenetic mechanism of "microangiopathic hemolytic anemia." It has recently been shown that disseminated intravascular coagulation may be a factor of significance in the pathogenesis of acute renal failure in glomerulonephritis, certain patients with cirrhosis of the liver, vascular surgical operation causing regional ischemia with recirculation of blood, hyperacute rejection of renal homografts, hyaline membrane disease, fat embolism, malignant hypertension, and the postpartum hemolytic-uremic syndrome.

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GIVE CASTOR OIL FOR "ATHLETE'S FOOT"

"I advise patients who have fungus infections on their feet . . . to soak their feet twice weekly for 15 minutes in a warm foot bath containing two tablespoons of household chlorine solution, such as Chlorox, and to put castor oil between their toes after each bath. The castor oil works simply by penetrating the dead or the chorionic layer of the skin, and the fungus cannot grow on it."

—MARK M. MARKS, M.D., Kansas City

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The Clinical Importance Of Pharmacogenetics

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* This morning Dr. Charles Becker, who is the Senior Medical Resident, will discuss certain aspects of pharmacogenetics. He will present some brief case histories to illustrate these points.

DR. BECKER:† Thank you, Dr. Smith. Unfortunately this topic is too broad for thorough discussion of the vast number of clinically important pharmacogenetic problems. McKusick in his recent compendium¹ listed some 1,500 diseases with presumed genetic transmission. Although many of the problems encountered in pharmacogenetics appear to be rare and unusual, the number is increasing rapidly as physicians learn to recognize that therapeutic intent may be greatly influenced by genetic factors.

Case Examples

The following case histories are taken from the UC Medical Center's hospital records and represent some recent problems in pharmacogenetics:

The first patient, a 25-year-old woman, was given suxamethonium chloride, 50 mg, during an abdominal operation. The anesthetist noted that the patient remained apneic for three hours. This prolonged drug effect has been described in the literature and is now a well recognized syndrome of pseudocholinesterase deficiency.

The second patient, a 30-year-old woman, had hypertension and tuberculosis. Isoniazid therapy for tuberculosis was begun, after which severe pe-

ripheral neuropathy developed. She was also treated with hydralazine for hypertension and a severe lupus-like syndrome ensued, with positive tests for the lupus erythematosus cell. This patient was a "slow acetylator" of isoniazid, and toxicity to this drug developed because of a slow rate of drug metabolism. This reaction also illustrates that hydralazine, which actually was introduced as an antituberculosis drug, is metabolized by the same enzyme system (nonmicrosomal) as isoniazid. Patients who are slow acetylators have a higher incidence of the lupus-like phenomena which have been recognized as a complication of hydralazine therapy for hypertension.

The third patient was a 24-year-old man with severe head trauma and seizures. After he had received 600 mg of diphenylhydantoin (Dilantin®), pronounced toxicity with nystagmus, ataxia and confusion developed. There was no history of liver disease, and family members had a similar response to the drug in the same dose. This is an example of an enzyme defect altering a therapeutic response — a deficiency of the inducible microsomal hydroxylase enzyme responsible for metabolizing diphenylhydantoin. These patients have severe reactions to small doses of diphenylhydantoin. Phenobarbital may induce new formation of this microsomal hydroxylase. If patients are given both phenobarbital and diphenylhydantoin, metabolism of the latter may be increased.

The fourth patient, first described by O'Reilly,² was a 73-year-old man who had had a myocardial infarction for which anticoagulant therapy with warfarin was begun; 145 mg of warfarin was re-

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†Charles E. Becker, M.D., Senior Resident in Medicine.

TABLE 1.—Areas of Drug Metabolism Influenced by Genetic Factors

Absorption
Binding
Drug-Cell Interaction
Enzymatic Metabolism
Conjugation
Excretion

quired for adequate anticoagulation, a dose 20 times that normally required. The patient's identical twin and six other relatives (a three-generation age span) had a similar response to this drug. Despite this huge dosage, the patient was sensitive to vitamin K, administered to lower the prothrombin time. This represents an example of genetic resistance to a drug.

The fifth patient, a two-year-old girl, had a severe hemolytic crisis when treated with a sulfa drug for a fever of unknown origin. Her father gave a similar history, and all studies for glucose-6-phosphate dehydrogenase activity were normal. This problem was caused by an unusual hemoglobinopathy—hemoglobin Zurich. This example of a drug-induced genetic disease could have been missed had the diagnosis not been considered.

Introduction

The term *pharmacogenetics*, which was introduced into the medical literature by Vogel and Motulsky, may be defined as the study of genetically determined variants where the phenotype or the genotype are detected by drug effects. Although it has been recognized for many years that patient-environmental variation is important in determining drug effects, only recently has it been appreciated that genetic factors may play a large part in subtle drug-patient variation. Not all drug-patient variations can be ascribed to genetic factors, but the increasing use of metabolic blocking drugs and enzyme inducing drugs has heightened the clinical awareness of possible subtle pharmacogenic problems.

Vessell³ studied identical and fraternal twins in detail to help separate environmental from genetic influences. Age is an important factor in determining genetic and environmental influences. Drugs like chloramphenicol are not metabolized in the very young until the enzymes responsible for metabolism are fully developed.

There are several ways in which genetic and environmental factors interact to alter drug response (Table 1). Drugs may undergo biotrans-

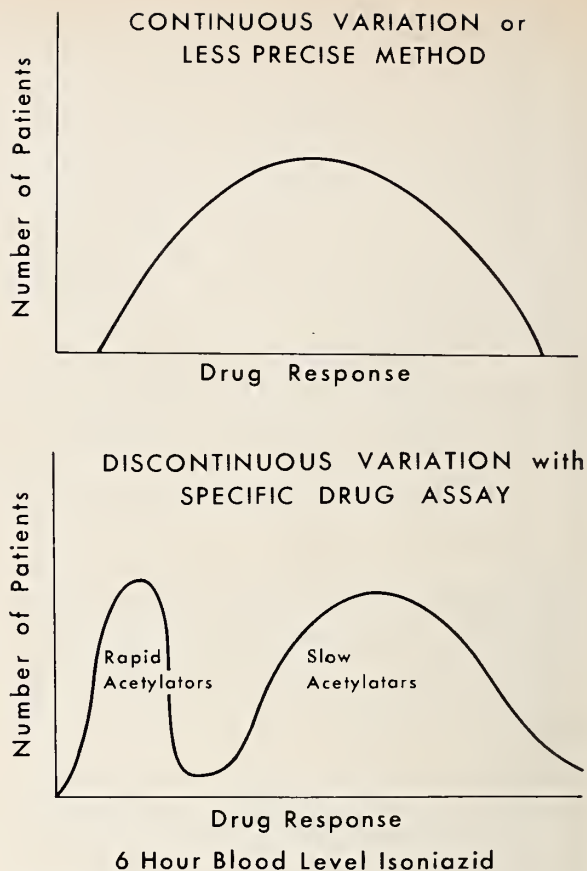


Chart 1.—Continuous and discontinuous variation with isoniazid therapy.

formation when the active ingredients are absorbed. Further changes can occur with binding of the drug to transport proteins; at the cell-drug interface; or with a number of metabolic reactions involving drug metabolism, conjugation or excretion. Clearly genetic and environmental factors interact during each of these steps and any minor abnormality could produce an unwanted effect.

Clinically, what clues indicate that we might be dealing with a specific genetic alteration of drug metabolism rather than an environmental one? If a given drug is administered in a standard dose and in a controlled fashion to large numbers of persons, three different variations are seen: (1) idiosyncratic reaction, (2) continuous variation, and (3) discontinuous variation (Chart 1). The idiosyncratic reaction may occur quickly as an untoward reaction in a very few persons with abnormal reactivity to the drug. The continuous variation results in a unimodal curve approaching a normal distribution; whereas the discontinuous variation gives a bimodal curve indicating almost

TABLE 2.—*Examples of Abnormally Prolonged Drug Effects Related to Genetic Abnormalities*

Drug	Clinical Problem
Suxamethonium chloride . . .	Prolonged apnea
Nitrites	Methemoglobinemia
Diphenylhydantoin	Ataxia, nystagmus
Allopurinol-6-mercaptopurine	Bone marrow depression
Isoniazid	B ₆ deficiency-neuropathy
Hydralazine	Lupus-like syndromes

complete separation of two or more distinct populations. If all environmental variables can be controlled, discontinuous variations may indicate a separate and distinct genotype. The parameter used to determine the variation is critical: If the parameter for drug response is the blood level of a drug, an inadequate method may suggest continuous variation while a more precise method might reveal discontinuous variation. For example, if one group of patients receives isoniazid, and blood levels are drawn and determined by a precise method at six hours, two different groups, rapid acetylators and slow acetylators, are observed. This is discontinuous variation. Carbohydrate intolerance induced by the thiazide diuretics is an example of continuous variation which may be discontinuous when more precise measurements of drug effects are developed.

There are several categories where discontinuous variation in drug action can be studied for identification of a specific genotype:

- Abnormally prolonged drug effect
- Increased sensitivity to a drug
- Decreased responsiveness to a drug
- Direct effect of a drug on the genotype

Abnormally Prolonged Drug Effects

There are a number of examples of prolonged drug effects related to genetic factors, many of which represent examples of discontinuous variation (Table 2). The abnormally prolonged effect of suxamethonium chloride in some patients with pseudocholinesterase deficiency was noted above.⁴ It is also recognized that nitrite-containing drugs oxidize hemoglobin and have been involved in the formation of methemoglobinemia. As noted above, diphenylhydantoin therapy in a patient with a deficiency of the hydroxylating enzyme may lead to a prolonged drug effect. The interaction between allopurinol and 6-mercaptopurine illustrates that certain new drugs with genetic influence may bring out latent pharmacogenetic problems. Allopurinol is a very potent xanthine oxidase inhibitor. Pa-

tients with a genetically determined xanthine oxidase deficiency, as in the drug-induced form, have a disease known as xanthinuria, which is suggested by a very low plasma uric acid level. In patients who are treated with 6-mercaptopurine, the xanthine oxidase system is necessary for drug metabolism. It is well recognized clinically that when a patient is given allopurinol, the dose of 6-mercaptopurine must be decreased in order to decrease toxic side effects.⁵ This is an example of a drug-induced enzyme inhibition which greatly prolongs the toxic effects of 6-mercaptopurine. The recent explosion of drug-induced enzyme blockade may lead to similar drug interactions.

Problems with isoniazid therapy represent an important area of pharmacogenetic research. Isoniazid was first synthesized in 1912 by Meyer and Malley and has been used extensively in treating tuberculosis. Isoniazid is rapidly absorbed orally, with a maximal blood level at two hours, and is metabolized in the liver by an acetylation reaction. In patients with slow acetylation, liver biopsy specimens have shown a deficiency in the enzyme which acetylates isoniazid. Despite this abnormality the renal clearance of the drug is normal. Whether the drug is given intravenously or by mouth, the acetylation changes are similar.⁶

There is a striking racial distribution in the activity of the acetylation enzymes for isoniazid. The Caucasian and Negro population of the United States contain approximately equal numbers of rapid acetylators and slow acetylators. In most Mongoloid populations approximately 90 percent of individuals are rapid acetylators. In the initial studies it was suggested that rapid acetylation may influence the response of these patients to therapy. This is, in fact, not the case. This drug has been studied and found to be effective in many patients who are rapid acetylators. Although the sputum may convert more quickly and the tuberculous cavities close more rapidly in slow acetylators, at the end of six months there is no difference in clinical response to isoniazid between slow and rapid acetylators. It is also true that the atypical mycobacteria have not been encouraged by slow or rapid acetylation; however, the side-effects of isoniazid have been increased strikingly in patients who metabolize the drug very slowly. Although vitamin B₆ is specific for improvement in neuritis, which occurs as a toxic effect of this drug, there are many unusual questions and problems that have been related to this phenomenon. Animals

and humans who are pyridoxine deficient exhibit a decidedly different syndrome from that seen in isoniazid-induced pyridoxine deficiency. It was originally suggested that vitamin B₆ itself increased the blood levels of isoniazid, but this apparently is not the case.^{6,7,8,9}

A number of other drugs whose metabolism is similar to that of isoniazid may also have increased toxicity if metabolized slowly. These include hydralazine, antidepressant drugs (phenelzine-monoamine oxidase inhibitor), and certain antibiotics (sulfamethazine); all may have increased toxicity in patients who are slow acetylators.

Increased Sensitivity to Drugs

Table 3 lists the drugs known to have increased sensitivity when given to patients with certain diseases, and those drugs which precipitate diseases. In an excellent Medical Staff Conference this year, Dr. Donald P. Tschudy from the National Cancer Institute spoke on the subject of porphyria. He has studied the induction of porphyria by barbiturates and other drugs. There is a genetically determined predisposition to glaucoma when topical steroids are placed in the eye. Increased sensitivity of hemoglobin Zurich to sulfonamides has also been reported. All of these reactions represent discontinuous variation of a drug response. Three reactions suspected of having discontinuous variation include glucose intolerance and increased uric acid as a result of thiazide administration, diabetes mellitus following glucocorticoid therapy, and Parkinsonism with phenothiazine treatment. At present these reactions appear to represent examples of continuous variation. With better criteria it may be possible in the future to demonstrate discontinuous variation with these drugs.

Glucose-6-Phosphate Dehydrogenase Deficiency

The problem of primaquine and glucose-6-phosphate dehydrogenase deficiency is perhaps one of the best known pharmacogenetic problems. In 1885 phenylhydrazine was first recognized as producing severe hemolytic reactions, and small precipitations of hemoglobin within red cells (Heinz bodies) were described. The 8-amino quinolone drugs, which are aniline derivatives and similar to phenylhydrazine, were later found to induce hemolytic anemia in certain racial groups. During World War II primaquine was given prophylac-

TABLE 3.—*Drugs Which Precipitate Symptoms in Genetic Diseases*

<i>Drug</i>	<i>Genetic Disease</i>
Barbiturate	Porphyria
Topical corticosteroid	Glaucoma
Sulfonamide	Hemolytic anemia Hemoglobin Zurich
Primaquine	Glucose-6-phosphate dehydrogenase Hemolytic anemia
Phenothiazine	Parkinsonism
Glucocorticoid	Diabetes mellitus
Thiazide diuretic	Diabetes mellitus Gout

tically to large numbers of military personnel in malaria infested areas. It soon became clear that a hemolytic reaction was occurring with the use of this drug. The gene frequency for glucose-6-phosphate dehydrogenase deficiency approximates 15 percent of the Negro population in this country and has a well defined geographic distribution similar to that of sickle cell anemia and thalassemia. Although a genetic defect in the red blood cell predisposes it to hemolytic anemia, the same defect offers relative protection from malaria. It has been speculated, although not proven, that the glucose-6-phosphate dehydrogenase deficient red cell is not a welcome environment for the malaria parasite.

Racial variability is very important in anticipating the degree of hemolysis. For example, Mediterranean people have a much greater predisposition to the hemolyzing effects of various drugs than do American Negroes. In Mediterranean people with glucose-6-phosphate dehydrogenase deficiency hemolysis may come about simply from inhalation of pollen from the fava bean. Often the problem is not recognized unless the hemolysis leads to jaundice.^{6,7,8,9} Recently at this Medical Center a patient was treated for gout with probenecid while receiving isoniazid and para-aminosalicylic acid for tuberculosis. With this therapy the symptoms of gout worsened. The patient was found to have glucose-6-phosphate dehydrogenase deficiency, and both probenecid and para-aminosalicylic acid have been associated with hemolysis in this enzyme deficiency. The chronic hemolytic anemia may have increased the uric acid turnover and worsened the gout.

The course of the hemolysis induced by glucose-6-phosphate dehydrogenase deficiency is an important example of practical pharmacogenetics. When 30 mg of primaquine is given to a susceptible patient, there is initially little evidence of abnormal-

TABLE 4.—*Decreased Responsiveness to Drugs Related to Genetic Abnormalities*

Drug	Clinical Manifestation
Vitamin D	Rickets, osteomalacia
Phenythiocarbamide	Thyroid disease
Suxamethonium chloride	No paralysis
Azathioprine in the Lesch-Nyhan syndrome	No decrease in uric acid
Atropine (rabbits)	No pupillary effects
Warfarin	Difficulty in anticoagulation

ity. Eventually hemolysis, hemoglobinuria and reticulocytosis develop, followed by gradual return to a stable chronic hemolytic state. Younger red cells have a relatively greater amount of glucose-6-phosphate dehydrogenase than mature cells which are more sensitive to hemolysis. Clinically this is important because in patients with acute hemolytic reaction the determination for glucose-6-phosphate dehydrogenase may be artificially increased because of a larger population of young red cells from the bone marrow.

The importance of detecting glucose-6-phosphate dehydrogenase deficiency for the prevention of malaria in combat personnel during both World War II and Vietnam has led to mass screening for this defect by many means. Initially glucose-6-phosphate dehydrogenase deficiency was detected by counting Heinz bodies. It has also been determined by directly measuring the enzyme but now is determined by other screening tests. The end result of this practical pharmacogenetics problem is the prevention of many of these reactions in combat personnel by anticipation of this adverse reaction. Glucose-6-phosphate dehydrogenase deficiency has also been a valuable marker allowing linkage determination of the x chromosome. Recently Dern and others¹² have described increased glucose-6-phosphate dehydrogenase in certain red cells. These patients are apparently normal by hematologic criteria. Overt cases of hemolytic reactions with glucose-6-phosphate dehydrogenase deficiency are easy to recognize, but this low-grade, drug-induced anemia may be quite subtle. One must first consider the diagnosis if the diagnosis is to be confirmed.

Decreased Responsiveness to Drugs

Genetically determined resistance to drugs is an increasing problem (Table 4). Recently vitamin D resistant rickets has been clarified and may represent a genetic type of drug resistance. An enzyme defect in vitamin D metabolism that prevents the

formation of active vitamin D may account for this syndrome. If the patient is treated with active vitamin D, this type of rickets may improve. I am particularly interested in patients who are unable to taste phenylthiocarbamide, which has a structure similar to that of some anti-thyroid drugs. Some patients who are unable to taste phenylthiocarbamide have a high incidence of certain types of thyroid disease.⁹ Suxamethonium chloride resistance has also been described as a genetic type of drug resistance.

Kelley and coworkers^{13,14} described in detail the metabolic defects in the Lesch-Nyhan syndrome and they found an enzyme deficiency (hypoxanthine-guanine phosphoribosyltransferase) which may explain the severe hyperuricemia, self mutilation and choreo-athetosis characteristic of this disorder. Azathioprine (Imuran®), which has been used increasingly in this hospital as an immunosuppressive agent, is a potent blocker of *de novo* purine biosynthesis and will decrease the serum uric acid level in most patients with overproduction gout. However in patients with Lesch-Nyhan syndrome, there is no decrease in purine synthesis following administration of this drug because of the inability to convert the drug to its active form. Kelley and coworkers also showed that allopurinol, a potent blocker of *de novo* purine synthesis, may not be effective in reducing the uric acid level if there is a deficiency of hypoxanthine-guanine phosphoribosyltransferase.¹⁵ Although this fortunately is a rare genetic disease, it illustrates a type of drug resistance which formerly was not recognized. It is conceivable that many minor enzyme defects may alter a patient's responses to many drugs.

Warfarin Resistance

Warfarin resistance was first recognized in the patient described in Case 4.² Two pedigrees of dominant inheritance of genetic resistance to coumarin drugs have been described. O'Reilly^{2,16} has studied this extensively and found that the protein binding of these drugs, the absorption, distribution, and biological half-life of warfarin is perfectly normal. This is in sharp contrast to a patient exhibiting a striking increase in metabolism of the drug as reported by Lewis.¹⁷ Patients who are resistant to warfarin may also be resistant to other anticoagulants—namely, bishydroxycoumarin and phenindione—even though the structure of these drugs differs from that of warfarin. Despite the fact that large doses of these drugs are required

TABLE 5.—*Genetic Diseases Associated with Chromosomal Abnormalities and Malignancy*

Down's Syndrome
Bloom's Syndrome
Fanconi's Anemia
Xeroderma Pigmentosa
Ataxia-Telangiectasia

for adequate anticoagulation, these patients are extremely sensitive to vitamin K.

What is the selective advantage of resistance to anticoagulant drugs? Why should an individual express resistance to a compound to which he has never come in contact? As you know, clover and many foodstuffs have biochemical properties similar to certain properties of the anticoagulants. Because of this similarity it has been speculated that warfarin shares an enzyme system normally required for the handling of these naturally occurring foodstuffs.

Drugs Directly Affecting Chromosomes

There are many environmental influences which affect genotype: Radiation, infection, poisons, nutrition, and perhaps hygiene may all affect chromosomes. Drugs have recently been implicated in altering genetic make-up by direct effects on chromosomes.^{10,18} With the vast improvement in cytogenetics and the concern with the relation of cytogenetic abnormality and teratogenicity, there has been much public concern with drug-chromosome interaction.

Much of the concern with drug-induced chromosome breakage results from the high incidence of teratogenicity and malignancy associated with five inherited disorders involving chromosomal abnormalities (Table 5). The first of these inherited disorders is Down's syndrome, a trisomy of the twenty-first chromosome. The risk that leukemia will develop is 20 times as great in these patients as in the normal population. Bloom's syndrome,¹¹ which is inherited as an autosomal recessive trait, is characterized by low birth height, stunted growth, and telangiectatic erythema. The cultured blood cells of these patients show a high incidence of chromosomal breakage. These patients often die as a result of malignant neoplasia. Patients with Fanconi's anemia,¹⁹ an autosomal recessive trait, have pancytopenia, increased skin pigmentation, mental retardation, and skeletal deformities. They also have a high frequency of chromosomal breaks and death resulting from leu-



Figure 1.—Photomicrographs of radiation-induced chromosomal damage showing quadriradial patterns similar to those seen in LSD studies. (Photograph courtesy of Dr. Sheldon Wolff, UC Medical Center.)

kemia and solid malignant neoplasms. Xeroderma pigmentosa is a rare hereditary disease and an autosomal recessive trait in which the skin is unusually sensitive to even slight sunlight exposure. This disease has been under intensive study since there is an apparent defect in the desoxyribonucleic acid repair mechanisms.²⁰ The disease is also associated with an increased frequency of chromosomal breakage. Death often occurs at an early age because of metastatic cancer. Finally ataxia telangiectasia, a disease characterized by cerebellar ataxia, recurrent infection, and death at an early age secondary to leukemia or lymphoreticular malignancy, has also been associated recently with an increased frequency of chromosomal breakage.²¹

Recently in the mass media LSD (D-lysergic acid diethylamide) has been implicated as a prime offender in damaging chromosomes. Grossbard and coworkers²² reported an instance of leukemia associated with a Philadelphia chromosome in a patient who had taken LSD over a long period. Zellweger and coworkers²³ described unilateral fibular aplasia in an infant born of parents who had used LSD. These reports, of course, have caused much concern. There are many drugs which may influence chromosomes; obviously it is quite likely that patients who have exhibited increased chromosomal damage have also taken many drugs other than LSD. On the basis of such limited studies, it would be unfair to implicate LSD specifically. This prob-

lem is important to study, but the evidence that LSD is teratogenic is not yet conclusive.

The most disturbing feature about LSD is that the drug apparently causes unusual types of breakage rarely observed in normal persons.¹⁰ Although normal cells in tissue culture may have a small amount of chromosomal breakage, LSD when placed directly in tissue culture or when taken by mouth is associated with the so-called quadriradial breakage pattern (Figure 1). This pattern is exceedingly rare in normal persons.

In conclusion, I would stress the importance of looking for discontinuous variation of drug action and would hope to raise your clinical suspicion that untoward drug effects may have a pharmacogenetic explanation. It is likely, with the many new drugs released and the great awareness of drug-chromosome interaction, that pharmacogenetics will become even more important in the management of patients.

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DEALING WITH NEWSPAPER REPORTS OF MIRACLE CURES

"When the grandparents of a child [with a chronic or fatal illness] insist on the parents showing the physician newspaper clippings or magazine articles concerning miraculous cures discovered in some remote town in Texas or a uniformly successful treatment concocted in New England, the physician should not act in a condescending manner. He should take the article, write the author, and ask him to send an immediate reply. Invariably, the author writes back that he was badly misquoted and really has nothing new. When these reply letters are shown to the parents and they show them to their families, the heat is turned off; and the physician stands in the proper position of having been quite willing all along to pursue any conceivably hopeful lead."

—JAMES G. HUGHES, M.D., Memphis

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The Wilson-Mikity Syndrome

Case Report and Review of Literature

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■ *The Wilson-Mikity Syndrome is a newly described respiratory ailment of very premature infants. It is typified by its characteristic clinical course, with onset after a period of well-being, and radiologic findings of coarse infiltrates alternating with cystic changes. At least four cases have occurred in the last two years at the University of California Medical Center, San Francisco. An exemplary case is given. The pathophysiology of the syndrome appears to relate primarily to abnormal ventilation perfusion relationships resulting from uneven lung compliance. It is suggested that the syndrome results from a distortion of the normal development of the fetal lung.*

ATTENTION HAS BEEN DRAWN recently to a newly recognized disease of premature infants that was first described in 1960 by Wilson and Mikity¹ at the Los Angeles County Hospital. Since then approximately 100 cases have been reported.²⁻²³ The disease has been variously labeled,^{2,4,5,8} but is generally referred to as the Wilson-Mikity syndrome. The syndrome occurs characteristically in very premature infants, usually weighing 1,500 grams or less at birth and with a gestational age of 30 weeks or less, although two cases have been reported in full-term infants weighing 3,100 grams and 3,700 grams at birth.^{8,11} Mikity, et al¹² report an incidence of approximately 1:450 premature

(2,500 grams or less) deliveries. The incidence appears to be much higher in infants weighing less than 1,500 grams at birth and probable or definite evidence of the syndrome was seen in more than half of 52 premature infants weighing less than 1,300 grams at birth.¹¹ There is no association with age or parity of the mother, complication of the pregnancy, or race or sex of the infant.

Clinical Course

The infants often have transient respiratory distress at birth due to asphyxia or occasionally to hyaline membrane disease. Such distress clears (or is not present at all) and strikingly, the infants almost always do well for several days up to over a month; (in one of our cases onset of symptoms did not occur until the forty-first day). The syndrome can develop within hours of birth, however. There is gradual onset of intermittent or continuous cyanosis requiring continuous oxygen therapy,

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Figure 1.—At six days. The chest film shows foci of small cysts interlaced with coarse, streak-like infiltrates, typical of Stage I.



Figure 2.—At ten weeks. There is persistence of the cystic changes and reticular infiltrate in the upper lung fields. Cysts have coalesced to form blebs in the bases, which are hyperlucent and hyperexpanded. The picture is typical of Stage II.

tachypnea, and moderate retractions. The respiratory difficulties commonly increase in severity for two to six weeks. The electrocardiograms of many of the affected infants show developing right ventricle hypertrophy. Right heart failure may occur. The infants usually feed well and gain weight normally. Therapy is purely supportive and consists primarily of increased atmospheric oxygen tension; steroid treatment has not been shown to be beneficial. Approximately 75 percent of the affected infants survive. If an infant lives past six months, it will almost surely recover. Survivors improve gradually and are usually well by one year of age. There do not appear to be any long-term residua.

Radiologic Findings

The radiologic findings are characteristic; diagnosis can be made without biopsy.¹² The findings change as the disease progresses, and several stages have been described.^{8,12} The first stage appears with onset of the clinical syndrome and consists of foci of cysts 1 to 4 mm in diameter throughout the lung fields, interlaced with coarse, streak-like infiltrates, 0.5 to 1 mm thick, giving the lung a "bubbly" appearance. There are no cardiovascular abnormalities.

The second stage can present two different sets of abnormalities. Mikity, et al¹² reported a second stage beginning at approximately six weeks and consisting of enlargement of the cysts at the bases to form blebs. The lower lobes become hyperexpanded and hyperlucent, and the diaphragms are flattened. Cystic changes and the reticular infiltrate persist in the upper lung fields. Alternatively,

Grossman⁸ told of a pattern of coarse streaks radiating from the hilus and extending particularly into the upper lung fields. Cystic foci were no longer present, though the lungs appeared decidedly hyperaerated. Second stage changes in our cases were similar to those described by Mikity, et al.¹²

In the third stage, there is complete clearing of the abnormalities, occurring from three months to two years after the onset.

Report of a Case

At least four cases of the Wilson-Mikity syndrome have occurred during the last two years at the University of California Medical Center, San Francisco. Diagnosis was made by characteristic clinical course and radiological changes. The x-ray films in the series of Mikity, et al¹² were reviewed and the radiologic findings in these four infants were believed to be consistent with that series. All infants were born prematurely, the largest having been 1,200 grams at birth, and all have survived. A representative case is briefly outlined here.

The patient was a white female weighing 850 grams at birth after 26 weeks' gestation that had been complicated only by slight first trimester bleeding. Delivery was normal. Hyaline membrane disease, with typical x-ray changes, resolved by day 4, at which time the baby was doing well and was intermittently in room air. On day 6, Stage I radiologic findings developed (Figure 1) with accompanying lethargy, retractions, tachypnea, cyanosis, and oxygen dependence. Steroid treatment

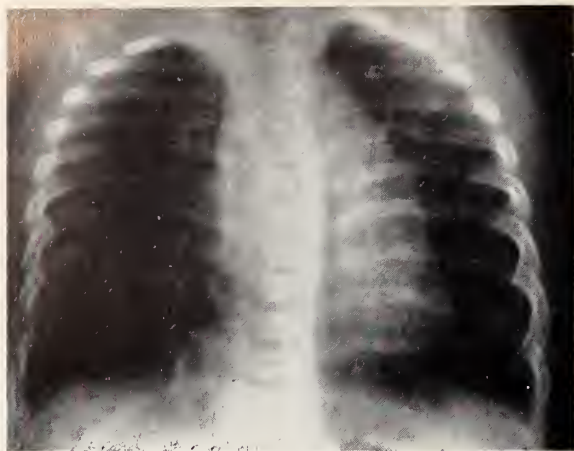


Figure 3.—At 1½ years. The x-ray is much improved, but it continues to show stringy infiltrates and hyperinflation.

was begun on day 28 without apparent improvement. There were numerous apneic spells. At ten weeks Stage II radiographic changes, as described by Mikity, et al,¹² were seen (Figure 2). An electrocardiogram at this time revealed signs of right ventricular hypertrophy. The patient began to improve by four months, oxygen tension was gradually lowered to that of room air, and the infant was discharged at five months. Roentgenographic abnormalities were resolving at that time. Multiple cultures, throughout the hospital course, were negative. At seven months of age there was an increased pulmonic closure sound and prolonged expiratory phase of respiration. At one year of age there were no respiratory signs, although pulmonic closure was still loud at 1½ years. The last roentgenogram, at 1½, was much improved but continued to show stringy infiltrate and hyperinflation (Figure 3). Weight gain was normal and the patient was doing well.

Pathology

Numerous biopsy and autopsy reports permit pathological description.^{1,13,24} The lungs are of normal weight. Grossly, they show an alternating pattern of pale, aerated and darker, depressed areas, early in the course of the disease. Later they have a typical, emphysema-like, hobnail appearance. They are grossly hyperaerated and remain inflated at autopsy.

I have had opportunity to review the histologic sections of Hodgman et al.²⁴ Most striking is the relatively normal appearance of much of the sections. Many areas appear altogether normal.

Others appear hyperinflated with rupture of septa and are adjoined by regions of collapse with juxtaposition of septa. In many places, the mesenchyme is thickened with a mononuclear infiltrate composed of several cell types, including some fibroblasts and even some smooth muscle cells. Such mesenchyme resembles that found in very immature, non-aerated lungs. Some reports emphasized fibrotic changes,^{1,2,7,10} but fibrosis is now considered to be a small, unimportant part of the pathologic manifestation.^{8,12,14,24} The greater fibrosis seen by some investigators may have been due in some cases to residua from hyaline membrane disease,²⁵ and in others to oxygen therapy.²⁶

Functional Changes

The functional disturbance in the Wilson-Mikity syndrome appears to be primarily uneven ventilation with consequent abnormal ventilation-perfusion relationships.¹³ This hypothesis is suggested by the discrepancy between measurements of "dynamic" and "static" lung compliance. Pulmonary compliance can be measured in several ways. Under ideal conditions it is measured when there is no air flow ("static" compliance). This can be achieved by having the patient hold his breath at different degrees of inspiration while intraesophageal (that is, transpulmonary) pressure is measured. But in infants this procedure is almost impossible to perform, for it depends on waiting until the infant spontaneously holds his breath. Moreover, there is no guarantee that cessation of air flow at the infant's mouth is not due to closure of the glottis rather than breath-holding.

Hence, compliance of infants' lungs is determined by continuous recordings of pressure-volume curves during normal tidal volume swings, without breath-holding ("dynamic" compliance). Values of pressure and volume at points of no air flow, that is, at end-inspiration and end-expiration, are used so that values will not be distorted by pressure needed to counteract resistance to air flow.

Until the 1950s and the work of Otis, et al,²⁷ it was generally believed that static and dynamic compliance were pretty much one and the same; and indeed in healthy persons this is true. But in adults with pulmonary disease, such as emphysema and asthma, values of dynamic lung compliance obtained are much lower than those of static lung compliance. Measurements of dynamic compliance in infants with the Wilson-Mikity syndrome are low,^{6,7,13} as the sub-costal and inter-costal retrac-

tions would suggest. Although compliance varies directly with lung volume (hence the use of "specific" compliance, that is, compliance/functional residual capacity, for comparing compliance in different individuals), it has been shown that a reduction in lung volume does not account for the decrease in compliance.^{6,13}

On the other hand, static compliance was normal when measured in an anesthetized, curarized infant with the syndrome,¹³ and as shown at autopsy.⁵ Here, then, is the same discrepancy between measurements of dynamic and static lung compliance as seen in adults with some types of lung disease. As Aherne and coworkers¹³ pointed out, the work of Otis, et al²⁷ affords a solution to this apparent incongruity. These investigators consider lung units and their airways as analogous to electrical RC (resistance-capacitance) circuits. Each unit has a resistance (to air flow) and a compliance (capacitance). These form a product which is a constant (for that particular lung unit) and which has the dimension of time (compliance \times resistance = ml/cm H₂O \times sec/ml \times cm H₂O = sec). An increase in the compliance or resistance of a lung unit will increase the value of the time-constant — that is, that particular unit will take longer to empty and to fill. If some time-constants are longer than others, measurements of dynamic compliance will be low, since those units with long time-constants will not have had time to respond completely to change in pressure, and air will continue to flow into and out of them (from and to units with shorter time-constants) at end-inspiration and end-expiration, respectively (so-called "pendelluft"). In this case, the dynamic lung compliance is not a valid estimate of the true lung compliance (though it does reflect respiratory work), but is indicative of variation in length of time constants in various parts of the lung. Alveolar ventilation is then uneven, since different parts of the lung require different amounts of time to empty and fill. Units with very long-time-constants will never completely empty and fill. Aherne et al¹³ expressed belief that the consequent unequal ventilation-perfusion relationships and hypoventilation are responsible for the respiratory symptoms in these infants.

Additional findings support this belief. First, several observers have reported a reduced "crying" vital capacity^{9,13} (although Baghdassarian, et al⁵ reported it to be normal), but static inflation volume, determined under general anesthesia¹³ and at

autopsy,⁵ was normal. The conclusion can be drawn that the rapid respirations during crying do not allow the lung units with long time constants time enough to fill. Second, these infants have CO₂ retention and resulting respiratory acidosis. Increase in PCO₂ can be caused only by hypoventilation of at least part of the lung, presumably that part with long time-constants. Third, the finding that the arterial desaturation is at least partially correctable with 100 percent O₂,^{7,13} suggests that at least part of the lung is being hypoventilated. There do not appear to be any anatomical shunts,⁷ and the fact that the PO₂ is only partially correctable by 100 percent O₂ implies a ventilation-perfusion defect of major proportion, though it is probably due in part to shunting through atelectatic areas. Fourth, lengthened time-constants would result in air trapping, which was found on post-mortem examination.⁷ These findings all provide very convincing support for the hypothesis of Aherne et al.¹³

Burnard and coworkers²⁸ examined serially 33 premature infants weighing less than 1,800 grams at birth. At least ten of the infants showed abnormalities of respiratory function similar to those seen in the Wilson-Mikity syndrome, including very high resistance to airflow, early air trapping (as suggested by a drop in thoracic gas volume at one to two weeks, confirmed in premature²⁹ and full-term³⁰ newborns), a fall in dynamic lung compliance by two weeks of age only in part accountable by the drop in thoracic gas volume, and a moderate increase in PCO₂ by two weeks of age. In addition, seven of the infants showed roentgenographic changes similar to those described in the syndrome, although in no case did these changes progress to the "bubbly" appearance characteristic of the syndrome. In a recent study, Thibeault, et al¹¹ reported radiologic findings either definitely or probably typifying the syndrome in 35 of 52 infants and abnormalities similar to those seen by Burnard, et al in 13 others weighing 1,300 grams or less at birth. These findings suggest that the Wilson-Mikity syndrome results from an exaggeration of abnormal respiratory function present in all prematures.²⁸

Etiology

Infection appears to have been ruled out as the etiological factor. Multiple cultures from all sites have been negative, as reported by many investigators, with only two exceptions: Type 19

ECHO virus was isolated in one case,⁵ and Type 7 ECHO virus in another.¹⁴

Some investigators, reporting significant amounts of fibrosis, now no longer thought to be a part of the histologic manifestation (as was previously noted) sought to differentiate the syndrome from the Hamman-Rich syndrome. The Hamman-Rich syndrome has indeed occurred in young infants.^{7,10} However, emphysema-like cyst formation never occurs in the Hamman-Rich syndrome, fibrotic change and septal thickening is far more prominent in the Hamman-Rich, and survival is usual in the Wilson-Mikity but unusual in the Hamman-Rich syndrome.⁷ Moreover, Hamman himself reviewed the histologic sections in Wilson-Mikity syndrome and considered them to be different from those in the Hamman-Rich syndrome.²

Thibeault, et al¹¹ suggested that oxygen toxicity may play an etiologic part in the Wilson-Mikity syndrome. They cited evidence that biopsy sections in two cases of Wilson-Mikity syndrome show changes like those produced by oxygen toxicity. Indeed, radiologic findings associated with oxygen toxicity are similar to those seen in this syndrome.³¹ However, there is strong contradictory evidence. Northway, et al²⁶ examined pathologic sections from the lungs of infants treated with respirators and high oxygen tensions for long periods (more than 156 hours). Their pathologic findings, consisting primarily of mucosal dysplasia and sloughing, increased mucus secretion, subsegmental overdistention, lymphatic dilatation and bronchiolar smooth muscle hypertrophy are not characteristic of the Wilson-Mikity syndrome. In addition, in the series of Hodgman et al,²⁴ which now numbers more than 30, some of the infants were never exposed to high oxygen tensions before the syndrome developed.

Burnard, et al²⁸ noted that the tracheobronchial tree is very compliant in premature infants, as shown by post-mortem examination of excised specimens. They suggested that focal collapse of small bronchi on expiration might occur even at very low transmural pressures. This phenomenon would not only explain many of the functional changes in premature infants, but it could also result in cyst formation (behind collapsed airways). This suggestion, however, is based only on extrapolation of data from larger to smaller airways. In addition, one would expect the smaller bronchioles to be supported by the lung paren-

chyma itself (in unexcised specimens), preventing collapse. Nonetheless, the hypothesis remains to be confirmed or disproved by further experimentation.

Mithal and Emery³² found that formation of alveoli in prematures living over a week after birth was decreased by as much as 25 percent in comparison with more mature stillborns of comparable age. They suggested that this reduction in the quantity of alveoli might be the cause of the respiratory distress in the Wilson-Mikity syndrome. Building on this postulate, Baghdassarian, et al,⁵ introducing the term "pulmonary dysmaturity," suggested that parts of the lung parenchyma might mature more rapidly than others. Alveolar proliferation might occur in some areas and fail in others. Where it failed, thick, relatively non-distensible septa would result. Where it occurred, septa would be normally distensible. Or in still other areas some compensatory mechanism might result in increased distensibility. Hence, there would be variable degrees of compliance throughout the lungs, which would explain the functional findings. The concept of "dysmaturity" is appropriate in that it allows for eventual maturation and recovery; but as Aherne et al¹³ pointed out, it is difficult on this basis to explain the onset of the syndrome within a few hours of birth in some infants.

Craig³³ mechanically expanded lungs taken post-mortem from very premature infants, including some under 1,000 grams who died at or shortly after birth. In those babies septa were thickened with mesenchyme: expansion was uniform, but compliance was reduced below that of older infants with thinner septa. These findings suggest compliance is directly related to septal thickness. In the Wilson-Mikity syndrome, then, compliance (and therefore time-constants) might vary from one part of the lung to another because of different septal thicknesses.

To understand further how "pulmonary dysmaturity" might develop, a brief review of the normal development of the prenatal lung is given here. Prenatal growth of the lung can be divided into three periods: (a) glandular — up to four months, (b) canalicular—4 to 7 months, and (c) alveolar—starting at six months.^{34,36} Lung formation begins very early in fetal life as an outpouching of the foregut ventralward. This outpouching branches into a right and a left mainstem bronchus, which in turn divide through many generations.

This branching growth occurs amid a matrix of very cellular mesenchyme. At first, the pulmonary branches are widely separated by connective tissue. As growth continues, there is a relative reduction in the mesenchyme separating the bronchi, which now grow closer together.³⁷

Branching of the non-respiratory bronchial system is complete by ten to sixteen weeks. The lung appears glandular because its air spaces are "blind"—they are completely lined by uninterrupted, columnar epithelium and enveloped by solid mesenchyme.^{34,35,38}

The canalicular stage commences at approximately four months as the diameter of the lumen of the "glands" begins to increase. Plank,³⁹ working with non-retracted lungs, that is, lungs fixed *in situ* in the thorax before post-mortem retraction can occur, described this transitional stage. As lumina enlarge, the tissue between them becomes stretched and its epithelial lining is lost. As enlargement continues, the septa separating canaliculae become attenuated and eventually rupture, so that large canals are formed. Broken elastic fibers from these septa continue to protrude into the lumen, their ends thickened and contracted. (Loosli and Potter,⁴⁰ in a widely cited article, suggested that these projections represented new, developing elastic fibers.) The canaliculae do not then arise from glands that are already formed. Instead, a new system of canals is hollowed out within the existing solid tissue by tissue breakdown.

It is tempting, then, to hypothesize that "pulmonary dysmaturity" develops as a distortion and exaggeration of the normal process of canalization. This process is not always finished by the time a fetus weighs 1,500 grams,³⁹ and most of the infants with Wilson-Mikity syndrome are this weight or less at birth. Respiration has been shown to result in narrowing of septal walls; Craig³³ reported on premature twins who died at different times: the first died shortly after birth and had thick septa; the second died several days later, by which time the alveolar walls were as thin as those in a full-term infant. Presumably, this might be due to a quickening of the process of canalization caused by the constant stretching and relaxing of the respiring lung. Septa, already attenuated at this stage, would break down both more quickly and in greater quantity. As excessive breakdown occurred, cyst formation would occur in some places. If ventilation were even slightly uneven at birth

(as is reasonable to expect, in view of intensified atelectasis in the premature,⁴¹ and diaphragmatic breathing²⁸), canalization would occur at different rates in different regions of the lung. In under-ventilated areas, thick septa would persist; in others septa would be of normal thickness; in still others, they would break down to form cysts. The resulting changes in compliance would perpetuate the process. As canalization continued, the syndrome would eventually develop, in hours, days or weeks. Canalization is seldom finished by term,³⁹ making understandable the occurrence of the Wilson-Mikity syndrome in full-term infants.

Support for this hypothesis is provided by the pathologic findings in two cases, reported by Weber, et al,¹⁰ in which there were broken septa with splintered elastic fibers, barren of epithelial cells, their thickened ends protruding into alveolar lumina — which fits the conditions described by Plank.³⁹

For further etiologic understanding of the Wilson-Mikity syndrome additional investigations are needed concerning the effect of respiration on the thinning of the connective tissue septa and their rupture as part of the transition from the glandular to the canalicular stage of growth.

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EMERGENCY MANAGEMENT OF MASSIVE UPPER GASTROINTESTINAL HEMORRHAGE

"Of particular value in the emergency management of patients with massive upper gastrointestinal hemorrhage is rapid passage of a nasogastric tube, particularly if the person hasn't had hematemesis. It's vital to know whether there is blood in the stomach on admission to the hospital. Also the tube can be used therapeutically with periodic irrigation of an iced Maalox and saline mixture; and the tube can be kept on suction which gives information regarding rate of bleeding and whether the bleeding has stopped. Finally the nasogastric tube can be used to remove acid and pepsin from the gastric contents. . . .

"I've mentioned some therapeutic uses of the nasogastric tube, but it has diagnostic uses, too. The tube can be put down and aspirated at selected levels—namely, the lower esophagus and the stomach; and if no blood is found in the stomach, it means either that the bleeding is stopped or that the site of bleeding is below the pylorus—coming, of course, from the duodenum or the upper small bowel."

—DOUGLAS A. FARMER, M.D., New Haven
Extracted from *Audio-Digest Surgery*, Vol. 16,
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scription series of tape-recorded programs.

University of California, Los Angeles, School of Public Health

THE UCLA SCHOOL OF Public Health, in common with its 14 sister schools in the United States, faces a particularly complex challenge in the education of students. The challenge comes from the necessity to provide the kind of instruction that will prepare students as public health professional practitioners of the future, in an era of continuous change, and in a field which is highly diversified.

Lacking a blueprint for the future, the educator in public health at best can make only thoughtful projections and must continuously assess and reassess the problem of what to teach that will have some permanent or enduring value. A few general principles are, however, apparent. The education of public health professionals is concerned with the progressive acquisition of knowledge from several disciplines, and the development of reasoning and judgment derived from the humanities and from experience.

Some professionals in public health come primarily from one general science area such as the biological, physical, or behavioral sciences. Others have some education and experience in several sciences, with greater depth of knowledge in one. Since modern social pressures are for the "team or group" approach to functions, then it is reasonable to expect that the professionals with the broadest education in the sciences and humanities, and with the broadest experience, will be the ones to provide group and community leadership in the health field. However, technical competence and knowledge, alone, do not make the public health professional; the most highly "educated man" is of little value to society unless he has some understanding of people's needs and especially their aspirations. Fostering the development of such understanding is an important part of the education of students who will be the public health professionals of the future.

The diversity and expansion of activities that characterize the field of public health today are phenomena of the present century. Public health efforts in the United States at the turn of the century were directed largely toward the control of morbidity and mortality from communicable diseases. Remarkable progress was made in this connection through advances in scientific knowledge of the causes of many communicable diseases and the systematic application of control measures, notably environmental sanitation and immunology. These efforts still continue, but the nature of modern life has added new dimensions to public health and has greatly increased the complexity of health and welfare problems. Further advances in scientific knowledge, a heightened sense of social responsibility, an increase in public expectation and demand, and major innovations in public policy are significant forces influencing the nature of public health both now and in the future.

The scope of public health today includes all activities which promote the health of the community and its individual members. It seeks a comprehensive approach to health problems, including the prevention, treatment, and rehabilitation of physical and mental illness, and the control of biological, physical, chemical, and social stresses in the environment. Areas within the field of public health in which expansion has occurred in the present century include medical care, occupational health, maternal and infant health, health of the school-age child, health of the older adult, mental health, chronic disease, nutrition, health education, rehabilitation, and several new facets of environmental health. In spite of the diversity of areas, however, the field of public health still remains a comprehensive entity involving the total health of populations and of various sociocultural groupings.

Although public health has developed its own body of knowledge and language, a large number

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of different disciplines contribute to its scientific nature. Various branches of medical science such as bacteriology, virology, and genetics are of fundamental importance. Other disciplines such as epidemiology and biostatistics have developed to serve the particular needs of the field. The social nature of public health requires the utilization of social science disciplines, including sociology, psychology, anthropology, political science, economics, education, and law. As might be expected, these roots in many and varied disciplines are reflected in a strong multidisciplinary emphasis in the curricula which schools of public health offer their students.

History and Setting of the UCLA School of Public Health

The University of California "state-wide" School of Public Health was established by the Board of Regents in 1944, with headquarters on the Berkeley campus. In 1954, a "southern section" of the school was recognized by the Academic Senate and established on the UCLA campus. The administrative structure of the "state-wide" school was very complex, with the associate dean of the UCLA "southern section" reporting to the campus administration and through the dean at Berkeley to the president of the University. In 1961, the UCLA "southern section" became an independent School of Public Health by action of the Board of Regents. The establishment of a separate school at UCLA provided for a single department with channels of communication and decision-making directly to the UCLA chancellor, vice chancellors, and Academic Senate committees. A significant parallel event in 1961 was the accreditation of the UCLA School of Public Health by the Committee on Professional Education and by the Executive Committee of the American Public Health Association.

Over the years, the UCLA School of Public Health has also undergone a striking evolution in its physical facilities and resources. Before 1961, the school was housed in a temporary barracks building known as "3T." Although composed of war surplus structures, "3T" had a main building and three wings and almost 9,000 square feet of space. It provided for some of the faculty offices; an administrative office; laboratories for biostatistics, microbiology, and health education; and a limited library. However, bench-laboratory research and teaching space was extremely limited,

curtailing the development of curricula requiring laboratory facilities.

In 1960-61, the school moved from "3T" to a concrete and brick structure built in 1954, which formerly housed the Department of Home Economics. This building provided about 35,000 square feet of usable space, and enabled the development of new laboratories for research and teaching. However, growth of the school occupied the building fully by 1963 and necessitated moving into several additional buildings both on and off campus.

In April 1968, the school's faculty, students, and research programs moved from these several scattered locations to a new building which is part of the UCLA Center for the Health Sciences complex. The present School of Public Health Building has nine floors (seven above grade and two below joined at all levels to the Center), a 130-foot north-south wing, a 180-foot east-west wing, and a gross floor area of approximately 125,000 square feet. Since the building was designed specifically for the School of Public Health, it has appropriate classroom, "wet" and "dry" laboratory, and office space.

The school's present location in the UCLA Center for the Health Sciences is particularly advantageous not only because it provides for sharing many facilities but also because it affords the opportunity to consolidate mutual interests of faculties and students. The School of Public Health has easy access to the basic science departments of the School of Medicine as well as the clinical departments and the resources of the schools of Dentistry and Nursing, various special institutes, the hospital, and ambulatory care facilities. The School of Public Health has maintained a close relationship with the School of Medicine's Department of Preventive Medicine and Public Health ever since the department was established in 1953, and this association is now facilitated by their juxtaposition. Through joint appointments, some School of Public Health faculty work with medical students and graduate physicians as members of the faculty of the School of Medicine, and both faculties actively promote the pooling of academic and research resources. The Center for the Health Sciences also provides two resources which are used by the school daily: one is the Health Sciences Computing Facility, which is indispensable in the conduct of faculty and student research; the other is the Biomedical Library,

which has a collection of more than 225,000 volumes and about 6,300 serials (including holdings pertaining specifically to public health) and serves as the principal library resource for the school's students and faculty.

Other obvious advantages accrue to the School of Public Health from being part of a campus which comprises 14 schools and colleges, 71 departments of instruction, and 38 research units and programs. The location of UCLA in a large metropolitan area of a populous state, with a diversity of challenging socioeconomic and technical issues, stimulates faculty and students to participate in community life. Research, experimental demonstration, and service participation in community issues is extensive, covering a range of modern problems which stem from expanding technology, increasing population density and communication, and changing attitudes. The School of Public Health, itself, has established close cooperative arrangements with the health community throughout California, thereby providing numerous training and research possibilities. Such opportunities are also enhanced by the school's access to diverse populations ranging from metropolitan Los Angeles to rural Mexico.

These various favorable circumstances and events — autonomy, accreditation, assignment of new facilities, and advantageous location, among others — have provided an environment attractive to prospective students, faculty, research and non-academic personnel. The result has been a rapid growth in curricula, faculty, student body, and research as well as the attraction of substantial extramural financial support.

The Curriculum and Degree Programs

Academic planning at the School of Public Health, as in most American universities today, must cope with complex interrelationships of systems—administrative, academic (including teaching, research and community service), and non-academic. A fourth element is increasingly in evidence, namely, student organization and interest. The objective of this planning is, of course, a broad public health instructional program that has usefully high standards and at the same time serves society's public health needs and requirements.

The school's educational program emphasizes the historical perspective of present-day public health; the present and potential contribution of many disciplines and professions to the field of

public health; balanced academic programs of basic and theoretical studies in conjunction with applied sciences; and curricula to stimulate student initiative and curiosity. Through appropriate required and elective courses that stress broad exposure to basic issues as well as intensive study in selected specialties, the school's programs of instruction provide opportunity to develop understanding of the theoretical foundations and philosophy of the field of public health, and permit specialization in areas of professional service, research, or teaching. Because of multidisciplinary concerns, programs of study are available to students whose academic preparation has been in one of various physical, biological, or social science areas; for example, bacteriology, medicine, nursing, dentistry, veterinary medicine; engineering, mathematics, statistics; sociology, psychology, economics, political science.

Until 1955, the school's emphasis was on a four-year undergraduate program leading to a bachelor of science degree in public health, and many of the B.S. graduates went on to degrees in medicine and dentistry. In 1957-58, the emphasis shifted to master's and doctoral programs, and a number of the B.S. graduates subsequently returned to the school to enroll in these graduate degree curricula. The school is now discontinuing its bachelor of science program and is accepting new students in this program only if they can complete the requirements for the degree by September 1971. However, undergraduate courses in public health will continue to be available as electives or in preparation for the graduate degree programs.

At present the school offers graduate-level degree programs leading to Master of Public Health (M.P.H.), Master of Science (M.S.), and Doctor of Public Health (Dr.P.H.). A series of areas of specialization (majors) is provided within each of these degree programs. In addition, the school offers the degrees of Master of Science in Biostatistics and Ph.D. in Biostatistics. The curriculum for the M.P.H. degree was approved in 1954, and in 1955 the University of California Northern and Southern Legislative assemblies approved legislation for the Dr.P.H. degree for the "state-wide" School of Public Health. Programs providing for the M.S. degree were approved in 1956, and the program for the Ph.D. in Biostatistics was approved in 1958.

The M.P.H. and M.S. curricula include series of core courses which all students in these degree pro-

grams must take. Both cores include introductory courses in epidemiology and biostatistics, and the M.S. core in addition requires courses in research methods. The Dr.P.H. provides education for a higher level of professional service, research, or teaching in public health than is attainable through the master's level programs. A master's degree in public health or in an appropriately related field such as education, social work, psychology, physical or biological sciences is required, and two or more years of study beyond the master's degree is generally needed to complete the requirements for the Dr.P.H. degree. For persons with a previous doctoral degree in medicine or a related field, the total period of study may be reduced. In addition to choosing an area of specialization, the Dr. P.H. candidate also selects a "minor" area. Written and oral qualifying examinations are held near the conclusion of the academic preparation, and the Dr.P.H. culminates in a dissertation based on original research leading to a final examination.

The areas of specialization, or majors, offered are: Behavioral and Health Education, Biostatistics, Environmental and Nutritional Science, Epidemiology, Health Administration (Medical Care Organization and Public Health Administration), Hospital Administration, and Infectious and Tropical Diseases. There are also special curricula in International Health, Family Health, and Comprehensive Health Planning.

All degree programs have developed cooperative relationships with a number of other UCLA departments and schools. Depending upon their interests and career objectives, School of Public Health students take courses in one or more other departments, in some cases satisfying the requirements for the "minor."

The School of Public Health currently is developing plans for a program of graduate studies in public health for the Ph.D. degree (which will be in addition to the already established Ph.D. in Biostatistics). Similar to the other principal degree programs, the new program would provide for specialization in a series of substantive areas. The advent of a Ph.D. program will enable the school to place increased emphasis on education at the doctoral level, and in addition will permit two differentiated patterns of instruction. One pattern will be the M.P.H.-Dr.P.H. sequence, which will emphasize a broad spectrum of knowledge and the acquisition of professional skills, with the goal of high-level community health planning and service.

The other pattern will be the M.S.-Ph.D. sequence, which will focus on theory and depth of knowledge, with the goal of advanced research and teaching.

In addition to its regular degree programs, the School of Public Health has special provision for admitting students without an advanced degree objective—for example, persons employed in responsible positions in public health, and students preparing for foreign assignments. Such students may enroll in courses offered by other UCLA departments, and joint studies may be arranged to meet specific needs. Individuals who already have a doctoral degree may enroll in the school as post-doctoral scholars for special study leading to a Certificate of Postdoctoral Study. Although foreign students are admitted to the school's regular degree programs, some may be advised to consider graduate study and research without reference to a degree, if the time they have available for study is too limited to permit completing the degree requirements.

The School's Research Program

The School of Public Health faculty and students conduct a vigorous research program that cuts across the many areas comprised in the field of public health. An important element of the program is the training of students for professional research careers. The school's research projects are funded mainly by agencies of the Federal Government, principally the National Institutes of Health. Other federal agencies which provide support include National Institute of Mental Health, Children's Bureau, U.S. Department of Agriculture, Departments of the Army and Navy, National Aeronautics and Space Administration, U.S. Agency for International Development, and National Science Foundation. In addition, research support comes from private sources, including foundations and gifts from various donors. The school receives an institutional grant which is awarded on a formula basis by the Public Health Service to support health-related research and research training activities.

The school is headquarters for the recently established California Center for Health Services Research, a major endeavor now embracing five campuses of the University of California and several off-campus organizations. The Center's research program focuses on developing and testing criteria for determining the outcomes of health care.

Some examples of the research investigations that are conducted and supervised by individual members of the school's faculty are:

- Study of the economics of medical practice in the United States
- A series of surveys of national systems of medical care organization in various Latin American countries
- Study of criteria operative in the use of scarce life-saving equipment
- Nutritional interrelationships with genetic diseases
- Effects of amino acid deficiencies and imbalances on plasma and tissue amino acid levels
- Biogenic amine synthesis and blood studies in animals chronically exposed to carbon monoxide and magnetic fields
- Longitudinal study (since 1950) of the natural history and risk factors in coronary heart disease, cerebrovascular disease, and hypertension
- Prevalence and incidence of cervical dysplasia and cervical cancer according to use of oral and other contraceptive methods
- Study of arboviruses of medical importance in Indonesia
- Dynamics of *Culex tarsalis* and other mosquitoes of the southern Salton Sea area
- Survey of special, noninstitutional housing for older persons in California, and a test-control study of the effects of selected housing environments
- Study of the characteristics of users of marijuana in schools, colleges, and middle class communities in Southern California
- Analysis and specification of relevant social-psychological variables germane to intervention techniques in minority and disadvantaged communities
- Study of interpersonal communication and influence network systems in a Black ghetto community

Students, Faculty and Graduates

Student enrollment in the School of Public Health, following several early years in which it was relatively small and steady, began a pronounced increase after 1959. In recent years, enrollments have averaged about 350 students a year, approximately 50 of whom come from countries in all parts of the world outside the United States. From 1954 through June 1968, the school awarded a total of 730 degrees, 498 of

them at the graduate level and 232 B.S. degrees.

More than half the school's students receive financial support through traineeships which include stipends, tuition and fees, and travel. The largest source of funding for students is the Public Health Service; the next largest source is the National Institutes of Health. Other provisions for financial assistance include teaching assistantships and research assistantships, University fellowships, and residencies in preventive medicine for physicians. For students from other countries, fellowships are available from the World Health Organization, Pan American Health Organization, Organization of American States, U.S. Agency for International Development, and a few other sources.

For many years the School of Public Health students have had their own representative organization. It provides a means for communication with the dean and his administrative staff, stimulates useful dialogue between faculty and students, and contributes to the school's intellectual life by organizing and managing a colloquium throughout the academic year. In addition to this form of representation, there are also student representatives on several of the standing committees of the faculty.

The faculty of the School of Public Health, as might be expected, represents academic disciplines as diverse as the field of public health itself. The backgrounds of the faculty and professional research personnel encompass many specialties in medicine and in the biological and social sciences. In addition, a considerable number of professional persons who are practitioners in the health field have appointments in the School of Public Health. These persons also represent a wide range of specialties and contribute a valuable resource for the school, as well as a link to the professional and wider community.

The range of disciplines of faculty members as well as the school's general multidisciplinary emphasis are reflected in numerous interdepartmental, or joint, appointments. Joint appointments of School of Public Health faculty at present occur with the School of Medicine (departments of Biological Chemistry, Biomathematics, Medical Microbiology and Immunology, Medicine, Pediatrics, Preventive Medicine and Public Health, and Psychiatry), School of Dentistry, School of Nursing, School of Social Welfare, School of Engineering and Applied Science, and School of Business Ad-

ministration, as well as the Departments of Sociology, Psychology, and Political Science.

In addition to teaching and research responsibilities, the school's faculty members are called on frequently to serve on advisory groups and provide consultative service to local, state, national, and international agencies — both governmental and voluntary. The School of Public Health also accepts as a permanent responsibility the mission of helping to provide continuing education for public health professionals throughout the Southern California region, and wherever else such activities are not available. Toward this end, the school's faculty participates in a variety of short-term conferences, institutes, workshops, and courses, which are separate from the regular curricula and degree programs of the school.

The School of Public Health maintains a strong interest in its graduates, and frequently they are asked to advise or aid in some aspects of the school's activities. The school's alumni are most likely to undertake careers in government, often in local health agencies but also in state and federal

health agencies. They are also employed in hospital settings, principally in administrative positions; and a number are pursuing careers in college teaching or research, in business and industry, and in private health-related practice. The alumni have contributed several hundred articles to professional journals and have written books, monographs, and other publications. Several have been elected to major offices in national, health-related professional associations, and some have been recipients of various awards, honors, and other kinds of special recognition.

Although the School of Public Health is gratified by the successful products of its education, there is nevertheless a constant awareness that striving to improve its teaching programs must be an unending task. Curricula need continuously to be evaluated and revised with the aim not merely of following trends but rather of spearheading important new ones. The school is now in the most advantageous position in its relatively brief history to achieve these higher and broader goals.

LENOR S. GOERKE, M.D., Dean

GAUGING OXYGEN NEEDS OF BABIES

What recommendations do you have about giving oxygen to babies in respiratory distress for pediatricians who don't have access to elaborate facilities?

"I think there's no very good method of judging how much the arterial pO_2 is in the absence of an oxygen electrode. We advise people who ask us this question to give the baby an inspired level of oxygen 10 percent above that at which he is cyanotic. If the baby looks a little blue on 50 percent oxygen, then we would say give the baby 60 percent oxygen. We have found that the heart rate is a very valuable measure of anoxia or hypoxia. You can increase the oxygen by 10 percent increments until the heart rate levels off—for example, from a high of 160 or 170 down to 140 where one would like to see it. This again is a little bit hit and miss because a very sick baby may have a very low, fixed heart rate. Apart from cyanosis, I don't think there is a good method."

—JUNE P. BRADY, M.D., San Francisco

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EDITORIAL

Of Privilege and Disadvantage

THESE ARE TIMES when it is often an advantage to be "disadvantaged," as when seeking an educational opportunity for example, or to belong to a "repressed" ethnic minority if one is seeking certain kinds of jobs. This is true in spite of the fact that laws which were passed in recent years to protect the rights of just these disadvantaged minorities would seem to prohibit precisely this kind of discrimination. One hears words such as "justice," "dignity," "equality," "rights," "demands," "power," "reparations" and sometimes even "destroy" being used by certain militant minority groups who seek what they consider to be parity (and, some observers suspect, an even larger role) in American society. One senses that a trend is developing where the extremes of the social and economic scale are to be the privileged while the great majority in between may be approaching underprivilege, and this in spite of the fact that it is they who do most of the work and pay most of the bills whether through taxes or otherwise.

In recent years the temper of the American people has been to eliminate both special privilege and special disadvantage as quickly as possible. Laws have been enacted and court decisions have been rendered to hasten the process. The thrust has been for greater freedom for individual expression and fulfillment on the one hand, and for equal opportunity and equal access for all on the other. It is tacitly assumed, though never actually spelled

out, that fulfillment for an individual should never be at the expense of the same right for others, and that equality of opportunity does not necessarily mean equality of accomplishment or reward. It also is obviously not intended that minorities shall rule, whether by force or otherwise, nor is it expected or possible that minorities shall by fiat disappear, since almost everyone in America belongs to a minority of one sort or another. In fact American society itself is a unique amalgam of these minorities.

Since special privilege is no more a part of the American ideal than is repression, it is therefore paradoxical and perhaps in the long run unwise for the minorities considered disadvantaged to strive for equality by seeking or demanding special privilege, whether this be through persuasion or threat of force. Not only is this means to the end logically unacceptable, it also produces an instinctive adverse reaction among those who are in the majority, who have the vote and who pay the bills, and who more often than not belong to some racial or religious minority which at one time or another was also disadvantaged, repressed or perhaps even persecuted.

The situation that is developing needs more understanding, and this as soon as possible. If special privilege is to be reduced or eliminated, this will not be accomplished by encouraging or condoning special privilege. If the majority is to rule then a minority cannot call the tune. The evidence on both the state and national scene is that the reaction of the majority, though silent and unorganized, is beginning to make itself felt. If more serious difficulties are to be avoided it is imperative that a balance be quickly struck between privilege and disadvantage, whether this be in medical care, in education or in society itself. Only as soon as this

is accomplished to the satisfaction of the silent majority may it be expected that some very much needed funds for medical care, education and other equally important purposes will again begin to flow. These are times when reason, not bias, must prevail. Physicians have an important responsibility to influence the course of these events, both in medicine and in society.

Pharmacogenetics

IN PART GENETICS is concerned with the study of the causes of biologic variation. One of the major expressions of biologic variation lies in the reaction of an organism to changes in the environment. In man the use of drugs represents the introduction from exogenous sources of substances which change the internal or external environment of cells. It is not surprising that the remarkable genetic heterogeneity among individuals may be expressed now and again in differences in reactions to drugs. This is the topic of the Medical Staff Conference presented elsewhere in this issue. In a sense this topic is supplementary to that of drug interactions as a cause of unexpected action or inaction of pharmacological agents, a subject reviewed in detail in CALIFORNIA MEDICINE within the past year.¹

The interaction of genetic and environmental influences may be difficult to disentangle in the individual phenotype, a classical problem which has roiled and embroiled almost all who have ventured into these murky waters. In quasi-despair, and with chromosome in cheek, it has been stated as a rule of thumb that if a kid looks like his father, it is genetic; if he looks like a neighbor, it is environmental. It is increasingly clear that the genetic legacy of the individual spells out in nucleotide sequences not only the imprint of normality and the misprints of specific genetic diseases, but also the messages which allow for metabolic adaptation and defense. These encoded messages may also go awry, often best illustrated by the altered response to drugs.

Pharmacogenetics, a relatively recent field of scientific inquiry, is usually considered in terms of the influence of genetics on drug action. It might equally be concerned with the influence of drugs on genetic action, perhaps even of greater importance when more fully elucidated. The genetic endowment of the individual, expressed phenotypically in protein structure, configuration, and concentration, may alter drug action or reaction in several ways:

(a) There may be an alteration in drug metabolism *per se*. This is usually reflected in the intensity and duration of its action rather than in some qualitative alteration in response. The amount of the active agent available to its receptor site is altered (increased or decreased) because of genetically determined variations in inactivation, transport, or excretion. Deficiency of pseudocholinesterase will decidedly prolong the action of the muscle relaxant suxamethonium. In the absence of the drug the enzyme defect appears to carry with it no biological disadvantage.

(b) Genetic variation may have a direct effect on drug action. It is presumed that this represents an alteration in the receptor site such that the response to the agent is depressed (or enhanced) with no variation in its metabolism. The best example of this category of pharmacogenetics lies in genetic resistance to the action of coumarin as described by O'Reilly and coworkers,² and cited as one example in the Medical Staff Conference. It is intriguing to speculate that studies of such genetic variants may clarify the normal mechanism of action of this group of anticoagulants, now far from clear. Some of the best examples of presumed genetic alterations in receptor sites are in endocrinology, perhaps admissible in this discussion by considering hormones as natural product drugs. Pseudohypoparathyroidism, vasopressin-resistant diabetes insipidus and testicular feminization represent diminished to absent responsiveness to hormones as diverse in structure and function as parathormone, vasopressin, and testosterone, respectively.

(c) The adverse reactions to drugs may be altered (usually enhanced, although this may represent bias in ascertainment) by genetically transmitted vulnerability. The mechanisms involved may be very indirect. Some excellent examples of this have been discussed in the Medical Staff Conference: hemolytic anemia secondary to glucose-6-phosphate dehydrogenase deficiency, hemolytic

anemia by a completely different mechanism with the unstable abnormal hemoglobin Zurich, exacerbation of acute, intermittent porphyria by several classes of drugs including barbiturates and progestins. The link between drug and the adverse reaction may be obscure. The agents which exacerbate acute, intermittent porphyria induce the rate-limiting enzyme Δ -aminolevulinic acid synthetase in the liver and in this manner increase the synthesis of porphyrin precursors. But what links this to the neurological disorders? It is not known.

Another area of pharmacogenetics which is usually not considered under this heading lies not in the genetics of the host but of the target—for example, the pharmacogenetics of microorganisms in their susceptibility or resistance to antibiotic agents. Mutations in bacteria with environmental selection pressure from antibiotics are of obvious importance in medicine as micro-Darwinism. Transfer between bacteria by conjugation of resistance (R) factors, which are extrachromosomal genetic elements, complicates the interaction of drug and organism.³ Proper perspective, if not common usage, requires that passing notice also be given to this area for interaction of genes and drugs under the topic of pharmacogenetics.

As noted earlier, not only may genetics affect drug action, but also drugs may affect genetic action. This may occur phenotypically—for example, the competitive inhibition of xanthine oxidase by allopurinol. Of even greater importance, although much more obscure, this may occur genotypically as well. Most attention has been directed to carcinogens or acutely to such grossly teratogenic agents as thalidomide. In an era when we are constantly surrounded and invaded by alien molecules made up of contorted carbon atoms in food, drink, sprays, paints, and atmosphere, the potential action of these “inadvertent drugs” must give us concern.

Clinical pharmacology and human genetics have been two of the most active areas of medical investigation in the past decade. The marriage of these disciplines has produced a product of remarkable hybrid vigor.

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New Concepts in Cancer Control—Preventable and Avoidable Cancer

IT IS INDEED TIMELY that Dr. Wendell G. Scott, in the L. Henry Garland Memorial Lecture, has redirected our thoughts to the concept that most human cancer is preventable. All too often in recent years we have overlooked the possibility that many types of cancer—as in the instance of communicable diseases—may be prevented or avoided before we are able to solve the complexities of their induction and pathogenesis.

Certainly the concept of prevention of cancer is not new. Dr. Scott has reminded us of a classic example as early as 1775, when Sir Percival Pott linked the high incidence of scrotal cancer in chimney sweeps to soot, and instituted protective clothing and cleanliness as preventive measures. A discussion of new concepts should direct our attention to a review of etiologic factors as we understand them today, including physical factors such as radiation, chemical carcinogens, and other agents such as viruses.

As was so aptly stated by Boyland in 1967, “Cancer prevention is better than cure.” However, it is important to realize that “even if the causes of cancer were miraculously removed . . . cancer would still be occurring 50 years from now, owing to the long latent period between the stimulus and occurrence of the disease.”

One new concept to be stressed now is that prevention can be applied to many more types of cancer and to a much larger number of potential cancer victims than is at present being done. If, in fact, at least 85 percent of human cancer is attributable to carcinogens, the siren challenge is the prospect that human cancer in large part may be eradicated by the more precise identification of environmental carcinogens and their elimination, and that this might be achieved before the phenomena

pertaining to the conversion of normal to malignant cells are elucidated as a result of studies in the basic sciences.

In 1919, James Ewing, the great American oncologic pathologist, wrote: "The twentieth century opens as the experimental era with the systematic study of tumors throughout the animal kingdom, and it seems likely to be noteworthy as a period of specific etiologic investigation which promises to separate many neoplastic diseases formerly held to be closely related. It may thereby prove to be the era of successful therapeutics and prophylaxis."

Despite the enormous gains of the first 69 years of the twentieth century, the number of persons who die of cancer continues to increase. This paradox of an increased overall incidence and mortality in cancer in spite of our present unparalleled increment of knowledge is both sobering and challenging. Much remains to be accomplished, and especially in prevention.

At the time of Ewing's statement, a number of occupational hazards had already been identified and associated with greater than normal risk of cancer incidence, but the proportion of persons affected was small compared with the population at large. Extrinsic chemical and physical carcinogens (for example, x-rays, ultra-violet rays) had been identified with the induction of specific types of cancer. However, the pace of this kind of experimentation did not subsequently match the significant advances pertaining to our knowledge of cell physiology, subcellular structure, cell kinetics, molecular biology, nucleic acid chemistry, virology, immunochemistry, and chromosomal alterations.

Some of the historic observations are worthy of recapitulation here because they have led us step by step to our present knowledge of cancer prevention. For example, in the developing synthetic dyestuff industry, Rehn in 1895 associated the high incidence of cancer of the bladder among workers with aniline to their exposure to this dye. However, it was not until much later, in 1954, that Case and Pearson demonstrated that it was not the aniline *per se* that was carcinogenic, but the aromatic amine contaminants. In 1966 Case published an authoritative account of the occupational hazard from exposure to such aromatic amines (especially those with methyl radicals). The story of certain azo dyes as potentially dangerous food additives is now well known, thanks to the careful pioneer work of Yoshida (1935) with ortho amino-azobenzene, of Kinoshita (1936)

with butter yellow (4-dimethyl amino-azobenzene), and of Nelson and Woodard (1956) with o-aminoazotoluene and p-dimethylaminoazobenzene. The carcinogenic hazard of butter yellow as an additive to hairdressing oils such as brilliantine was demonstrated in 1962 by Williams.

The natural occurrence of carcinogenic substances in plants is more common than had been originally demonstrated, thus requiring closer scrutiny of epidemiologic observations derived from allopathic and veterinary medicine. For example, estrogens present in sufficient concentration in some varieties of clover cause reproductive disturbances in sheep. It has been suggested that even small amounts might facilitate the growth of estrogen-dependent mammary tumors in women. The fascinating story of the cycad seed, the possible relationship of its glycone and aglycone, and the attendant relationship of beta-glucosidase and intestinal bacterial flora have been the subjects of numerous investigations by Laqueur. Other carcinogens derived as natural products include those elaborated by molds such as *aspergillus flavus*, namely the potent hepatoma carcinogens aflatoxin B and G. Some naturally occurring products act indirectly. An example is the enzyme thiaminase occurring in the bracken fern in England, which is radiomimetic. In addition to destroying vitamin B, it contains a factor which causes leukopenia and increased capillary fragility. Recently, malignant intestinal tumors have been produced in rats fed a diet containing dried bracken.

It is now recognized that cancer may result from a host of different factors, some of which act singly whereas others act in subtle, complex combinations. A simple cause-and-effect relationship is illustrated by the action of certain nitrosamines which are relatively simple, open-chain, aliphatic compounds, so potent that the administration of a single dose is followed by neoplastic disease months or years later, at a site predictable in some animals and not predictable in others. In contrast, some neoplasms result from a more intricate etiologic relationship of several factors.

Both molecular biology and epidemiology are paramount for a realistic program of cancer prevention and a balanced program of research. Modern epidemiology will further the continued identification of extrinsic agents and their eradication from our environment. With respect to endogenously produced carcinogens, epidemiologic leads are likewise important in that they may sug-

gest the direction of research regarding the action of hormonal and nutritional factors.

Not only is a field approach essential in modern epidemiology, but it must be multidisciplinary, including environmental biology and biostatistics. There is general consensus that exogenous stimuli play a major role in most malignant neoplasms in man. The many new chemicals being synthesized each year for use in industry and medicine require careful evaluation with reference to their potential carcinogenesis. In 1963 it was shown that griseofulvin, an antibiotic very effective in the treatment of human fungal infections, induced hepatic tumors when administered orally to mice. The extrapolation to man of carcinogenic activity in experimental animals needs to be integrated with human environmental field studies. Isoniazid, a potent therapeutic agent, might well have been banned as a potential carcinogenic hazard if present testing regulations had been in force earlier, although the drug is apparently harmless to man at normal dose levels. In the absence of adequate supporting data based on environmental biologic standards, decisions regarding utilization of therapeutic and chemical compounds will continue to be made on an arbitrary basis, thus requiring society to live with situations involving calculated risks.

If epidemiologic research is to provide new knowledge in the foreseeable future, with practical implications in the field of public health, extensive collaborative studies in environmental biology will be essential. This means that biometry and tumor registries (cancer registries) must become participants and contributors rather than mere repositories of dead statistics. Inasmuch as differences in histologic pattern may be of etiologic significance, cancer registries in the future must be concerned with histologic analysis by age and sex for certain types of cancer (for example, bladder, thyroid gland, ovary, testis, and the reticuloendothelial system) so that "histologic age-specific rates" may be calculated. Another example of the role of epidemiology in cancer prevention concerns the study of migrant populations. Populations migrating from one environment to another may provide unique opportunities for epidemiologic studies of cancer since the genetic characteristics of such groups are initially unchanged. Such observations may be meaningful even though culturally determined environmental factors such as diet and the preparation of food may change very slowly over a period of years. Important leads have been ob-

tained recently, for example, from studies showing a contrast between the high incidence of cancer of the stomach in Japan and reduced incidence among migrants and their descendants in Hawaii and California, and also from studies of the increased incidence of cancer of the large intestine in Poles who migrated to New England urban areas rather than to rural areas.

The concept that highly carcinogenic agents occur as contaminants is one that cannot be lightly disregarded. The geographic variation in the occurrence of esophageal carcinoma has been a matter of perplexity for several decades. Often, its occurrence has been linked with the use of alcoholic beverages, as in certain—but not all—areas of Africa and Iran. Certain nitrosamines are highly selective carcinogens in the induction of esophageal carcinoma in rats. The recent demonstration of the presence of diethylnitrosamine in Malawi gin may be most significant; its presence signals the great need for a relatively simple screening method to detect such contaminants in alcoholic and other beverages and in foodstuffs. Such a method does not currently exist.

A controversial concept requiring critical evaluation is that the distribution of certain types of tumors in domesticated or wild animals in a given region is related to the distribution of human tumors in the same region. Currently this is being investigated by a human and animal population study in Alameda and Contra Costa counties in California.

Other epidemiologic-based studies, with connotations for prevention, are those concerned with neoplastic trophoblastic disease and with genital tract cancer in women. The peaks of high incidence of trophoblastic disease in women in the Philippines, in Malaysia, Singapore, and certain areas of Africa (tenfold greater than the incidence in Occidental populations) has been attributed to poor nutrition, to multiparity in the older age group, and to chronic illness. Recently, it has also been suggested that there may be a relationship with the degree to which the reticuloendothelial system of the women has been challenged by various antecedent infestations such as those due to plasmodia and leishmaniasis.

In the L. Henry Garland Memorial Lecture, Dr. Scott emphasized the great importance of the gains already obtained in reducing mortality from uterine cervical cancer, either *in situ* or invasive. This reduction in mortality has resulted from the increas-

ingly widespread use of the diagnostic Papanicolaou cytologic technique. Evidence from various epidemiologic demonstration case-finding studies during the past several years has suggested that carcinoma of the uterine cervix may be a venereal disease. As more is learned about the pathogenesis of cervical cancer and its precursors, it may be possible that this technique will also prove useful in identification of possible precursors of cervical cancer (for example, trichomoniasis, herpetic viral infection, dysplasia of squamous mucosa) while they are still curable or reversible. Thus the usefulness of the Papanicolaou cytologic technique may be extended and it may become valuable as a preventive measure.

Brevity permits only passing mention of additional concepts regarding etiology and implications for possible cancer prevention. These include (1) co-carcinogenicity (carcinogens—chemical, physical, and others, often weak, may produce neoplasms when acting together but not individually); (2) the multiphasic mechanism of carcinogenesis (some carcinogens may initiate a neoplastic process which remains dormant until other carcinogens promote or accelerate its growth); (3) intrinsic factors of oncogenic origin (in addition to extrinsic factors, hormones, genetic coding, and possibly viruses may be co-carcinogenic; although viruses are ostensibly extrinsic, some may be incorporated within the genetic substance of the cell, assuming thereby the role of an intrinsic factor); (4) etiologic viral agents (the ill-understood inducer role of certain viruses is becoming increasingly evident in certain neoplastic processes, particularly those of the lymphoreticular system, such as leukemia and Burkitt's lymphoma); (5) experimental vertical transmission of virus-induced neoplastic disease (this has been suggested, for example, by Gross with reference to murine lymphocytic leukemia and by Stewart with reference to a number of tumors of polyoma virus origin); (6) neoplasm induction in experimental animals by non-oncogenic human viruses (various DNA related viruses—for example, adenovirus, produce various malignant neoplasms in experimental animals); (7) hormone dependency (the growth rate of certain tumors, even when induced in animal mammary glands by chemical carcinogens, may be altered by hormone administration).

Looking to the future, the prospects are bright regarding the prevention of most types of cancer,

even before we fully understand the intricate intracellular processes that eventuate in their development.

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A Problem and a Proposal

A SERIOUS PROBLEM is developing which is no doubt a predictable outgrowth of the traditional employment status of interns and residents, a status which has too often resulted in their exploitation by both hospital administration and medical staff. For a number of years, it has been evident that the status of house staff, particularly their pay and fringe benefits, needed substantial improvement, but the response has been slow, and it now appears that it was too slow. A new determination by interns and residents to improve their status, compensation and working conditions is now apparent. This new determination is tough-minded and oriented to one kind of action which will very likely produce results. The new tough approach may be said to have started with the imaginative "heal-in" staged by the house staff at the Boston City Hospital a few years ago. This was successful and bore

results which were satisfactory to the house staff of that time. We are now informed that after a year or more of negotiations initiated by the Committee of Interns and Residents of New York City, a contract of labor union type has been entered into in New York City. A national association of interns and residents has come into being and in California a University of California Association of Interns and Residents has been formed and at the time of this writing is in negotiations with the five medical schools in the University of California system.

It is easy to react with pious indignation to all of this, particularly if one is old enough to compose an editorial for a distinguished medical journal such as this. But the facts are that things are different than they were 30, 20 or even 10 years ago. The majority of house staff is now married, often with one or more children. The length of their post-doctoral training has increased. They call attention to the fact that the income of most interns and residents is considerably below what is now held to be the level of poverty. They believe that they render service, sometimes very sophisticated service, and that they should be compensated with a living wage. They argue that specialized training in business, industry and even in other fields of graduate education is usually compensated more nearly adequately even though little service may be rendered.

The issues raised by all this extend far beyond the problem of reasonable pay and working conditions for interns and residents. Perhaps most basic is the question whether house staff should be considered hired help of the hospital, or are they actually professional people rendering the same professional services on the same patients as is the medical staff? On a broader scale, to what extent is it desirable to encourage the concept of hospital-based physicians who are employed by the hospital and paid from funds generated through the hospital daily rate for patient care? Is a very expensive hospital educational program a proper charge against a patient who is in the hospital for the care of his illness or repair of his injury? Can this all be justified on the basis of a better quality of care in a teaching hospital? And perhaps most important of all, what are the probabilities that this trend toward unionization among house officers may spread throughout the whole of the medical profession, as it has already begun to do in nursing, and will this be for the ultimate good or ill of the patient and the public? These are not easily answered questions, but must they not be faced and dealt with

by the medical profession right now? The alternative may be to permit a situation to develop which will not benefit the patient, the profession or the public.

In seeking a solution it is suggested that a number of factors which pertain to the problem be considered. The era of charity medicine is drawing to a close; in fact, the concept is probably no longer even viable. This end of an era was brought about by the enactment of Titles XVIII and XIX of the Social Security Act. However, these new titles and the regulations which administer them have not yet been able to resolve the inconsistency of trying to provide access to a single high standard of health care for all on the one hand and filling the needs for clinical "material" in teaching hospitals on the other. The difficulty is easily understood if it is recognized that "teaching patients" have traditionally been charity patients and this now conflicts with the aim to do away with charity in medicine. To reconcile this inconsistency it therefore seems only reasonable that if charity is to be phased out of the services of practicing physicians it should also be phased out of the services provided by licensed interns and residents in teaching hospitals.

It is proposed that a logical solution would be to recognize interns and residents as practicing physicians and members of the professional staff which, in teaching hospitals, would be organized as a group for the combined purposes of practice and teaching. Such a group would have appropriate internal arrangements with respect to privileges, responsibilities, working arrangements and compensations much as is the case with group practice outside of teaching institutions. If this were done, yet another step would be taken to remove "de-meaning" charity from medical care, the teaching situation would more closely parallel actual practice, the house staff would actually move into the mainstream of patient care, and the funds needed for support of the physicians involved, including the interns and residents, would generate largely and perhaps entirely from the services they render. The arrangements would be on a professional basis among professional people.

This proposal is a clear departure from the past. It would probably require changes in the Social Security law and certainly in the regulations. It would require revision of the wording but not necessarily the substance of the requirements of a number of the specialty boards and would cause practice groups to come into being in teaching hos-

pitals. But it all seems logical. It is almost certain that the legitimate demands of interns and residents will somehow have to be met, not only in California but across the nation. The necessary funding will be substantial and will have to come from somewhere. If charity medicine is really to be a thing of the past, professional groups, which would include licensed interns and residents, should be permitted and encouraged to collect reasonable fees for services rendered in a teaching situation just as is done in practice. Let us hope that it will do so promptly.

It is suggested that the American Medical Association is the appropriate body to assume the leadership needed to unravel this complex problem.

What and Where And When to Learn

AN EXPANSION OF the listing of Continuing Medical Education Activities begins in this issue of CALIFORNIA MEDICINE. The listing is designed to provide physicians with a current catalogue of all continuing medical education opportunities throughout California and in Hawaii, projected three to four months in advance. This section will continue to bring together in one place the announcements of meetings and courses, major grand rounds, radio and television presentations, Audio-Digest and all other available educational activities, listed by specialty and giving the date, the sponsor, the location, the address for further information, and the fee. In addition specific program information will now be included to assist physicians in preliminary consideration of what to learn and where and when to do so.

By centralizing information regarding all of California's continuing medical education opportunities the Committee on Continuing Medical Education of the California Medical Association is now coming to a position from which to achieve coordination by offering a clearing house service for program sponsors. Sponsors are invited to consult the system regularly to avoid conflicts in planning programs and to aid in revealing gaps and reducing duplication. It is hoped that resulting coordination will ultimately lead to more efficient use of the resources of faculty and funds as well as of physicians' time.

Therapeutic Abortion And Mental Health

UNWANTED PREGNANCY causes one of the most severe psychological stresses in a woman's life. It seems logical, therefore, that under the new abortion law, the great majority of therapeutic abortions (86 percent) have been done to preserve the mental health of the mother. With the technical advances of modern medicine, there are relatively few physical conditions that necessitate an interruption of pregnancy. Mental illness is the most widespread and depleting public health problem in our society. Since the appearance of its various forms almost invariably follows a precipitating stress, the appearance, recurrence or exacerbation of mental disease at the time of pregnancy is most understandable.

There are many factors in the stress of unwanted pregnancy, some internal and characteristic of the individual and her particular circumstances, and some external, emerging from our society and its attitudes. This environment is hostile in varying degrees to the woman who does not want to be pregnant, and particularly to the one who, whether married or unmarried, wishes to get rid of that pregnancy. If unmarried, she is further condemned for "immoral" behavior, and continuation of the pregnancy is often seen as a justifiable punishment. The criticism, disappointment, rejection and ostracism, whether real or fantasied, originating from those persons most important to the woman are stresses with which she must cope.

And what of the internal factors? There is an obvious struggle between the protective feeling, so universal in women, toward the concept of giving birth to a new life and one that will live on after her, and the panic of helplessness and hopelessness at the reality of her predicament. Pregnancy can have many different meanings to a woman and always necessitates adjustments, emotional as well as physical, which the emotionally handicapped or potentially handicapped woman may not be able to make, at least without depletion of her mental health.

What kinds of conscious, or unconscious, motivations lead to a woman's becoming pregnant and then desperately not wanting to bear the child? To the young the event may be due to ignorance, or it may be a demonstration of adulthood, a gift to a parent or a passport from a stifling home situation. An unwanted pregnancy may be a confirmation of a woman's femininity, a proof of "having been loved" or a trap for a desired man. It may be due to contraceptive failure, whether human or mechanical. The defenses which individuals use to protect themselves make the true motivations of this condition often unclear.

Hence the burden of assessing the probable effects of continuance of the pregnancy falls to the physician, who in turn must help the woman weigh her own often ambivalent feelings. One of the controversial aspects of the situation is the undeniable effects of sociological factors on an individual's mental health. The stress and consequences of an unwanted pregnancy as they affect mental health must be determined for an individual patient, taking into consideration her total life situation. Factors such as marital status, family support, economic conditions, subcultural attitudes toward the pregnancy, and personality structure all contribute toward her ability to maintain and complete her pregnancy without damage to her mental functioning.

The new law requires physicians to make judgments that are difficult to make, impossible to prove and of crucial importance to the patient's welfare and the welfare of those dependent on her and intimately involved with her. The burden of responsibility on the psychiatrist and the gynecological surgeon are great, particularly with the time pressure of advancing pregnancy.

Diagnoses of the mental disorders have fallen into almost every category, even that of homosexuality, with a preponderance, in most series, of psychoneurotic depressive reaction, emotionally unstable personality trait disturbance, schizoid personality pattern disturbance, and schizophrenic reaction of the chronic undifferentiated type. Psychometric tests have yielded helpful data in many cases. In a series in our University of California Clinic, the scales most frequently elevated on the Minnesota Multiphasic Personality Inventory (MMPI) were those of psychopathological deviancy, depression, schizophrenia and hypomania. Goldberg's Psychoticism Index on this test showed 52 percent in the psychotic range and 29 percent

in the neurotic range, with 18 percent indeterminate.

A follow-up study of a group of these patients is now being concluded, which includes a second MMPI three to four months after the initial one, and a comprehensive interview and questionnaire with the social worker. The data have yet to be analyzed and tabulated, but the subjective impressions recorded promise to be most interesting. One woman, the mother of six living children, reported that for the first time she felt like a person, and not like a factory.

A psychiatrist in San Francisco¹¹ has studied a group of 40 patients, whom he had judged to be in need of abortion on psychiatric grounds. Twenty-five percent of these patients had had previous psychiatric care, 25 percent had made suicide attempts or gestures before the pregnancy occurred, and 65 percent had made threats of suicide since the pregnancy had been recognized. In an 80 percent returned questionnaire at three to four months, there were no serious psychiatric sequelae. Guilt feelings at two weeks were reported to have been absent by 18 of the 40, mild in seven, moderate in three and severe in four. At three to four weeks, the report shifted to absent in 29, mild in two, moderate in none and severe in one. The attitudes toward a repeat of the same course of action were 81 percent affirmative without reservation; 13 percent unsure; 3 percent negative; and 3 percent said they would repeat the procedure only outside the law—illegally—the latter a comment on the toll of our often traumatic procedure of investigation and evaluation beforehand.

On a depression rating scale, the group mean score decreased by over 50 percent (a highly significant drop) between two weeks and three to four months postoperatively.

One important facet of this problem is the effect of therapeutic abortion itself on the mental health of the woman. At a public meeting when I commented on this consideration in some patients, Pat Maginnis, the abortion crusader, said, "Yes, there is a psychological reaction—relief!" Actually, carefully done studies indicate that serious psychiatric sequelae are minimal—Ekblad (1955),⁵ Simon (1966)¹⁵ and Peck (1966).¹³ Transient depressive reactions were common but selflimited, and, interestingly, one report indicated they were less common after abortions performed on psychiatric grounds than those due to other considerations.

Jerome Kummer in 1963⁸ reported that among

32 psychiatrists in the Los Angeles area, 75 percent had never encountered any moderate to severe sequelae of abortion, and the remaining 25 percent only rarely had met with serious post-abortion mental disturbance. He quoted a Copenhagen psychiatrist who stated that in 30,000 cases of induced abortion in 15 years, there were no serious sequelae. One problem in evaluating the literature is that European statistics usually apply to therapeutic abortion, whereas American studies include all types, spontaneous, induced and, in some, even illegal. When psychiatric sequelae are reported, resulting from an abortion, one must consider what sequelae might have emerged with pregnancy, delivery and either giving up or rearing the child. Truly, a pregnancy going to term is a life-long commitment for a woman. Giving up the child for adoption does not end the concern, and often it brings about self-recrimination. A therapy group of unwed mothers with whom I met for two years voiced these longings poignantly, and some celebrated the birthday of their lost infants, wondering what sort of life they were experiencing.

It seems, therefore, that abortion may prove to be the best course of the alternatives available to a patient. But it is almost never a complete solution to the woman's problem. The factors that were involved in the unwanted pregnancy must be understood and resolved if possible. Some degree of guilt and sense of loss almost invariably exists in the woman. The underlying psychological problems that have either been involved in her allowing herself to become pregnant, or at least have caused her to be unable to adjust to it, must be treated.

This poses a problem for all of us in the medical field. Follow-up psychotherapy in some form is often not available, or if so is unacceptable, due to economic problems, geographic difficulties, family factors and other reasons. With the decrease in anxiety occasioned by symptomatic relief of the pregnancy, motivation to continue therapy is often lacking. I believe that by working with the women in group therapy on a crisis basis for the two weeks before, during and following the abortion, we might guide more of them to continuing therapy. With such a program we might avoid the tragedy of subsequent unwanted pregnancies.

We must also help women avoid this defeating situation. Physicians caring for families and children can help parents to develop better relationships with their children, thus increasing the child's sense of identity and worth, and guiding him to

more stable mental and sexual maturity. The parents' task in this fast-moving, fast-changing world is awesome, and professional help is often crucial.

Comprehensive family life and sex education in the schools can prepare youth for more responsible sexual behavior and responsible parenthood. Family planning information and availability need to be greatly extended, so that pregnancy can be a choice made by individual parents, according to their own beliefs.

Perhaps we as a society have been asking the wrong questions. Could we ask instead, "Does an unequivocally unwanted pregnancy *help* any woman? Does birth as an unwanted child give a *fair* opportunity to any child?" Prevention of unwanted pregnancy is far more humane than treatment of it. This more positive approach could lead to a more enlightened day, in which we would deal with the problem of prevention of unwanted pregnancy, rather than its interruption.

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LETTERS to the Editor

Professional Corporations

To the Editor: Wide publicity has been given to the recent announcement of the Internal Revenue Service that it will now recognize many professional corporations formed under state statutes "as corporations for tax purposes." The Information Release of August 8, 1969, issued by the IRS is quite specific and I attach a copy hereto.

You will note that professional corporations substantially identical to those corporations recently litigated by the Federal Courts will be "let alone" by the IRS insofar as the issue of corporate recognition is concerned.

The decision of the IRS quite obviously removes the most menacing hurdle from the use of the corporate form by physicians, dentists and attorneys. However, the IRS recognition of professional corporations does not mean that *every* physician should immediately incorporate.

There remain many legal and administrative problems connected with adoption of the corporate form of practice. Competent professional advice is still absolutely essential.

Physicians must understand that practicing as a corporation involves real alterations in their daily habits and total patterns. If the corporate form is just a "piece of paper" further trouble is guaranteed. IRS recognition of professional corporations removes opposition to the corporate concept but doesn't change the *regular rules* applied by the IRS to corporations generally. The physician must understand this fact before incorporating.

Finally, I still have reservations regarding the ultimate recognition of one-man professional corporations. The legal attack on the one man (or two-man) corporation is still available to the Internal Revenue Service, even though it has in general recognized professional corporations as corporations for tax purposes. Solo practitioners should carefully examine this possibility as well as the economics of corporate practice before formulating a decision on whether or not to incorporate.

HOWARD HASSARD

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California Medical Association

(See also Mr. Hassard's article, "Medical Corporations—Some Observations," *Calif. Med.*, 110:512-513, June 1969.—Editor.)

Internal Revenue Service—Technical Information Release, 8 August 1969:

The Internal Revenue Service announced today, in response to recent decisions of the Federal Courts, that it is conceding that organizations of doctors, lawyers, and other professional people organized under state professional association acts will, generally, be treated as corporations for tax purposes.

This action followed a decision not to apply to the Supreme Court for certiorari in the recent cases of *United States v. O'Neill*, and *Kurzner v. United States*. This decision was made by the solicitor general and concurred in by the assistant attorney general (Tax Division) and the commissioner and chief counsel, Internal Revenue Service.

Both of these decisions held that a group of doctors organized under state law was classifiable as a corporation for Federal tax purposes. Obviously, however, the government must reserve the right to conclude differently in any case that reflects special circumstances not present in *O'Neill* or *Kurzner*.

An earlier decision had been made not to seek certiorari in *U.S. v. Empey*, holding a group of lawyers organized under the general corporation laws of Colorado to be a corporation for Federal tax purposes.

Nor will the government further press its appeals presently pending in the 5th and 8th Circuits. These are respectively *Holder v. United States*, and *Wallace v. United States*. Also, no appeal will be prosecuted in any other pending cases decided adversely to the government on the same issue involving similar facts. Finally, all similar cases now in litigation or under audit will be reviewed to see if they should be conceded.

Implementing instructions will be issued to field personnel—if necessary on a state-by-state basis—as soon as possible. In addition, appropriate modifications of existing regulations will be required consistent with these decisions.

Drowning and Hyper-Ventilation Syndrome

To the Editor: I was recently involved in a death by drowning that makes me feel that hyper-ventilation syndrome is a not uncommon form of death. The exact circumstances make me feel that our standard forms of resuscitation need some important improvement. As an M.D. and certified NAUI instructor, I feel obligated to call attention to these facts.

I will recount the shocking and almost unbelievable death so that others may be possibly saved under similar circumstances. I was taking a friend on an ocean boat dive off Catalina in May of 1968. He had a fair amount of pool practice, but only one previous ocean dive.

He was a young (30-year-old) former athlete and in excellent physical condition, but had shown some moderate fear on his first dive, about four months prior. He had done some thrashing to reach the ship's ladder and complained of a moment's "blackout." This "blackout" was apparent to no one but himself, other than as a possibly dazed or exhausted expression, so not much was thought of it.

There was no apparent fear on the present dive. On entering the water, I re-checked his gear and he signaled "OK." I had planned to take him in to shore since it was a calm day and make a very gradual submergence, because on the previous day

he had experienced difficulty in getting down, claiming not enough weights (it was a two-day trip this time).

We snorkled over toward shore, picking clear spots through the kelp. We were about 150 feet from the boat and 50 feet from the shore. I was taking the lead since he appeared to want this and was about ten feet ahead when he called, "Hey, Doc, I think I'll go back to the boat." This surprised me because it was a beautiful day, nice clear water and we were almost to the shore.

I swam back to him and, by this time, he had swum out of the clear passage we were following, to the edge of the kelp (as though he were thinking of going in a direct line through the kelp toward the boat).

We faced each other about two feet apart. I asked him, "What do you want to go back for?" He did not remove the snorkel from his mouth or attempt to reply. He just looked at me. Under the circumstances, I felt it better not to push my question and decided to go along with his desire to return to the boat. I indicated going back through the clear passage instead of through the kelp. His breathing at this time sounded normal and there was nothing to indicate trouble. However, he turned toward the kelp and the boat instead of the clear passage.

I pulled him gently by the shoulder and again indicated the clear space. He again turned toward the kelp (there was about 15 to 20 feet of it and then clear water to the boat). The boat had stood a little off shore because of some current and rocks.

At this point I decided to be a little foresighted and get ready for trouble if it should come. There was no real reason to assume he wouldn't swim back to the boat without difficulty as he had done the day before. At the worst, I felt I might have to help him get untangled from the kelp or some such. I put two short puffs in my safety vest for slight added bouyancy, put the mouthpiece of my regulator in my mouth and looked up to see what my companion was doing. He was nowhere to be seen.

I looked under the water ahead of me in the direction he had taken, and there he was, about 6 feet ahead and 5 feet down, slowly sinking.

I swam down to him with a little extra hard kicking. The small amount of air in my vest was no real obstacle. He was not tangled in kelp but he was unconscious and I noticed when I got him to the surface, he was a little heavy (lungs already

filled with water and, perhaps, an extra weight on his belt). I wasted a little time getting his regulator mouthpiece in his mouth. I noticed a small amount of vomitus drifting from his mouth during this procedure. I then pulled the fill cord on his safety vest. I took the regulator out of his mouth since he obviously was not using it, filled his lungs once amply with mouth-to-mouth, and called to the boat for help. He could not have been under water for more than 40 seconds, yet he was completely unconscious and nonreactive.

The rest of the rescue operation was done very efficiently since there was another NAUI instructor aboard, and the skipper was very capable as were other members of the club (another M.D. was also present). Help arrived within a minute or two, during which time I continued to give a few mouth-to-mouth breaths. The rescue party brought several rubber inner tubes with nylon rope attached and we were pulled to the boat very swiftly. I continued mouth-to-mouth during this time and good inflation of lungs was obtained as I could feel the chest expand and air and water came gurgling out after.

Mouth-to-mouth and heart massage (approximately a 2 to 10 ratio) was commenced on the tail gate of the boat, with the victim in supine position, head back, jaw forward. Head was at times placed sideways to facilitate spillage of water from lungs on exhale.

At onset of this period on the tail gate victim was unconscious and pupils widely dilated. After 15 minutes of resuscitation on tail gate, victim did not respond and he was therefore lifted to deck of the ship where procedure was continued for another 20 minutes before he was pronounced dead.

Nearly every physician has seen numerous instances of what is called hyperventilation tetany in nervous patients who hyperventilate in an attack of anxiety. Typical treatment is simply to calm them down or have them breathe into a paper bag to prevent excess loss of carbon dioxide with resultant acid-base imbalance in the blood and body, and production of muscle spasm and possible sudden loss of, or impaired consciousness.

These are cases of very minor importance on dry land; but in the water, as probably in this instance, sudden loss of consciousness, impaired consciousness, or muscle spasm can be fatal.

Some people are much more susceptible than others, but loss of consciousness and muscle

spasm probably could be induced in almost everyone with sufficiently prolonged hyperventilation. Some hyperventilation is very common in instances where people become panicked in the water, and death from such a cause is probably not uncommon. Unfortunately, it has been labeled in the past as simply "accidental death from drowning."

Related loss of consciousness as in shallow water blackout or the old trick kids often play of taking a few deep breaths and holding it while someone else puts his arms around subject's chest with resultant disturbance of bodily chemical-physical mechanisms and sudden loss of consciousness, is familiar to many.

Autopsy in the present case showed no physical impairment except water in the lungs and "accidental death from drowning preceded by hyperventilation syndrome." Since I had been on several mountain-climbing forays with this young man in the months preceding his death, during which he was exceedingly vigorous and not easily winded, there can be little doubt as to the good condition of his heart and lungs.

A further important question now arises: Why should death have occurred in this young man in excellent physical condition? He was only under water for 40 seconds at the most. Mouth-to-mouth resuscitation was inaugurated in perhaps another 40 seconds. Heart massage was begun within three minutes. Good standard procedures were applied throughout. He should not have died.

I believe the answer is that an improvement in standard procedures is in order. A suggestion for a change that has occurred in my mind is that mouth-to-mouth resuscitation should be done as it was until the victim is on a solid platform, such as a boat or dry land; after which, I believe, he should be placed face down in the Shafer position, head turned to the side, airway clear, jaw forward. Pressure should be applied from behind on the lower ribs. If possible, the body should be on a gentle incline with head slightly lower to facilitate drainage of water. Pressure should be applied to the lower ribs intermittently for respiration. It is to be noted that such pressure, properly applied, also constitutes a form of heart massage. This should be carried on for about 30 seconds to clear the lungs of excessive water and then the standard procedure of mouth-to-mouth respiration with patient on his back, head thrown back, two respirations to ten presses of external heart massage should be carried out. I believe that if this had

been done instead of the procedure followed, this young man might well have recovered.

In reference to this above procedure it is well known that electrolyte imbalance and damage to lung tissue from aspiration of water, and not simple suffocation, are most often involved in deaths from drowning. Because of this fact it is felt that when the lungs are flooded, one has only six minutes in ocean water and four minutes in fresh water before changes in blood electrolyte balance cause irreversible changes in the body and brain and consequent death. I also refer you to the recent fascinating work done by Dr. Johann Klystra, the Dutch scientist, now working on the same research for the Department of the Navy. He expressed the opinion that death was not caused by fluid in the lungs in itself, but was due to electrolyte imbalance caused by differences in solutions in the lungs compared with the blood. He produced a solution which closely approximated the blood (like Ringer's solution), increased the oxygen content, and kept experimental animals alive for extended periods of time under water. When their lungs were drained, the animals were able to carry on without impairment. It therefore seems likely that the matter of removing fluid from the lungs becomes of paramount importance in the first four to six minutes.*

*The possibility of direct damage to the delicate tissue lining the lungs from foreign solutions like sea and fresh water which do not approximate the blood does exist.

Summary

1. A case of sudden death by drowning probably due to hyperventilation syndrome from panic was probably observed.

2. This is likely an unrecognized and not uncommon form of death from drowning and should be warned against.

3. Improvement of standard resuscitation procedures to include definite early clearing of the lungs of water to avoid electrolyte imbalance and damage to delicate lung tissue would seem desirable and probably imperative.

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*This last included to show that even in articles holding that removal of water from lungs to be of little importance, damage to lungs by water is considered very important.

CHRISTMAS CARD SALE TO PROVIDE AMA-ERF FUNDS

Doctors and their wives are urged to make their office and personal Christmas card selection from the wide assortment now available through most of the AMA-ERF chairmen of the county and district units of the Woman's Auxiliary to the California Medical Association. Simply call the county or district auxiliary president or AMA-ERF chairman to determine a time and place for viewing these original and especially selected designs.

The American Medical Association Education and Research Foundation (AMA-ERF) needs your purchase of these cards to provide financial assistance to the medical school of your choice, or for biomedical research.

If your county or district Woman's Auxiliary does not have the Christmas card catalogs and kits, or if it is inconvenient for you to see them, please write for a colorful and descriptive brochure and order blank which will assure proper credit of your purchase to your own county or district. Address this request to: Mrs. Albert E. Warrens, AMA-ERF Chairman, California, Woman's Auxiliary to the CMA, 2190 North Avenue, Chico, Ca. 95926.

Information

Cardiovascular Roentgenology: Conventional Studies

M. VIAMONTE, M.D.

Material Supplied by the California Heart Association

CARDIAC FLUOROSCOPY AND chest roentgenography complement history, physical examination and electrocardiography for the optimal evaluation of patients who have known or suspected cardiovascular disease.

Fluoroscopy is best accomplished by use of an image intensifier with optical or television monitoring. The major contribution of cardiac fluoroscopy is in the identification of abnormal calcifications, in the detection of abnormal cardiac contractility and in the analysis of chamber enlargement. Cardiac fluoroscopy also aids in the recognition of pericardial effusion and in analysis of cardiac contractility and great venal pulsation. Diaphragmatic mobility and changes in size of pulmonary nodules or masses when performing the Valsalva and Muller maneuvers may be observed via fluoroscopy.

Especially in infants, children and women in the child-bearing age, cardiac fluoroscopy should be conducted with minimum exposure and maximum patient protection. It is our policy to analyze the chest roentgenograms before carrying out fluoroscopic examination. A barium swallow study should be done as part of the fluoroscopic examination. Routine chest roentgenograms for cardiovascular evaluation at our institution include the following five films: (1) Posteroanterior chest roentgenograms without barium; (2) left anterior oblique view at 45° without barium; (3) right

anterior oblique view at 60° with barium; (4) left lateral view with barium, and (5) posteroanterior view, overpenetrated with barium. Because the heart is a three dimensional structure all these views are essential for complete evaluation of chamber enlargement.

Overall size of the heart is evaluated by the cardiothoracic ratio, which is the maximum transverse diameter of the heart divided by the maximum internal transverse diameter of the chest. This ratio should be less than 50 percent except in extreme obesity, or when elevation of the diaphragm causes the heart to lie in a horizontal position. Cardiomegaly may be misdiagnosed in the presence of a prominent pericardial fat pad. Such a pad is easily recognized by the relative translucency observed around the apex of the left ventricle at the left cardiophrenic junction. A pericardial fat pad may also exist at the right cardiophrenic angle.

In the posteroanterior view, the right heart border has two arches. The cephalad one is the vascular arch caused by the ascending aorta in adults, by the superior vena cava and right lobe of the thymus in infants and young children, or by the superposition of the ascending aorta and the superior vena cava in some persons. The caudal arch of the right heart border is formed by the right atrium.

The upper portion of the left heart border in the frontal projection is formed by the aortic knob (junction of transverse and descending portions of the thoracic aorta). The middle arch is formed by the left border of the pulmonary trunk (upper two-thirds), left auricular appendage (lower one-third), and the proximal portion of the left branch of the pulmonary artery. The caudal arch of the left heart border is formed by the left ventricle.

The left anterior oblique projection separates the left from the right heart chamber. These chambers occupy the anterior half of the heart. The posterior heart border is symmetrically convex and appears separated from the left bronchus by a radio-lucent area representing aerated lung parenchyma. The anterior half of the heart is occupied by the right atrium superiorly and the right ventricle inferiorly. A line extending the anterior border of the trachea divides the heart into two almost equal halves and usually indicates the plane of the interatrial and interventricular septa. The left anterior oblique projection is utilized during selective angiocardiology for the study of left-to-right shunts

Dr. Viamonte is from the Department of Radiology, Mt. Sinai Hospital, Miami Beach, Florida.

at the atrial or ventricular levels. Contrast medium injected into any of the left heart chambers, if seen to be directed anteriorly, indicates the presence of a left-to-right intracardiac shunt. This is also an excellent view for evaluating valvular, subvalvular or supra-valvular aortic disease. The left anterior oblique projection unfolds the thoracic aorta. Left ventricular outflow tract obstructions are best analyzed in this projection. This is the projection of choice for selective injection of the right and left coronary arteries. The right coronary artery is directed anteriorly and the left coronary artery posteriorly. The anterior descending division of the left coronary artery crosses the mass of the heart in the left anterior oblique projection.

The right anterior oblique projection is the view that separates the atria from the ventricles. The right anterior oblique projection should be taken at 60°. The reason for this is that it requires this degree of rotation of the patient to separate the image of the heart from that of the spine. The left and right atrium are projected posteriorly and the right and left ventricle are superimposed anteriorly. This view is most important in selective ventriculography for the evaluation of pathologic changes in the atrioventricular valves. It is also a very important view for the evaluation of the atrial enlargement.

The left lateral view of the heart separates the left atrium and left ventricle posteriorly from the right ventricle and right atrium anteriorly. In the lateral projection of the heart, on deep inspiration one usually sees a vertical line crossing the angle formed by the posterior heart border (diaphragmatic portion of the left ventricle) and the left leaf of the diaphragm. This line corresponds to the posterior wall of the inferior vena cava. When the posterior heart border projects dorsal to the caval line, this usually is indicative of left ventricular enlargement. The left lateral projection is of importance for the evaluation of heart size in the ventrodorsal direction, for the evaluation of left atrial, left ventricular and right ventricular enlargement, for the diagnosis of obstructive airway disease (diffuse obstructive pulmonary emphysema), and for the recognition of thoracic wall deformities such as sternal depression and the so-called "straight back syndrome." This is an excellent view for the analysis of the size of the primary division of the pulmonary artery. The right pulmonary artery usually projects as an oval shadow just caudal and ventral to the tracheal bifurcation. The

left pulmonary artery courses above and dorsal to the left bronchus.

The overexposed frontal view of the heart is of value for the recognition of abnormal cardiac calcification, for the detection of enlargement of the left atrium, for best localization of the thoracic aorta, and for the analysis of esophagus-heart relationships. The posteroanterior view of the heart is used for the evaluation of heart size in the frontal plane, and of cardiovascular configurations. The heart is said to have an "aortic or left ventricle configuration" when the left ventricular arch and the aortic knob are prominent. This determines relative narrowing of the waist of the heart (relative concavity of the middle arch of the left heart border). The "mitral configuration" is said to be present when the shadow of the aortic knob is small, the middle arch of the left heart border appears to be straight or convex, and the left ventricular arch is inconspicuous. The left heart border follows a straight line directed from midline to the left hemidiaphragm. A double density caused by left atrial enlargement and inversion of the pulmonary vasculature (upper, medial pulmonary vessels appear larger than lower medial pulmonary vessels) complete the picture of the "mitral cardiovascular syndrome." The "left-to-right shunt configuration" is said to be present when there is pronounced convexity of the middle arch of the left heart border and uniform pulmonary vascular plethora. "Fallout configuration" is said to be present when there is prominent rounding of the left ventricular border which appears raised above the diaphragm, the middle arch of the left heart border appears concave, and the shadow of the aortic knob is barely visible. This heart configuration is usually associated with pulmonary hypovascularity (secondary to right-to-left shunt). This group of findings is not pathognomonic of Fallot's tetralogy. It may be seen with other anomalies such as tricuspid atresia and persistent truncus arteriosus. The so-called "water bottle configuration" is said to be present when the right and left heart borders appear rather symmetric. There is enlargement of the transverse diameter of the heart. The pulmonary vasculature appears to be normal or decreased. This configuration is the consequence of massive pericardial effusion and of cardiac dilatation (primary and secondary myocardiopathy).

Of all the heart chambers the left atrium is the easiest to analyze. It is the most posterior chamber

of the heart and hence comes into contact with the esophagus. When the left atrium is enlarged, in the frontal projection one may see slight convexity of the lower third of the middle arch of the left heart border due to dilatation of the left auricular appendage. A disc-like density appears in the center of the heart and causes a double density on the right heart border and occasionally accounts for a third arch at the right heart border (the middle one). The interbronchial angle may appear to be widened (greater than 70°) when enlargement of the left atrium is directed superiorly. In extreme left atriomegaly, the esophagus may appear displaced to the right or to the left of the midline. Rarely, one may see atelectasis of the left lower lobe secondary to obstruction of the left lower lobe bronchus from a decidedly enlarged left atrium.

In the left anterior oblique projection the enlarged left atrium will obliterate the clear infra-bronchial space. One may see elevation of the left main bronchus. In the right anterior oblique projection the esophagus will no longer parallel the thoracic spine. Variable degrees of esophageal displacement may be encountered. Decidedly elongated esophageal displacement indicates pronounced left atrial enlargement, usually seen with severe mitral insufficiency. Localized, slight esophageal displacement indicates mild left atrial enlargement and predominant mitral stenosis.

Right atrial enlargement is best evaluated in the left anterior oblique projection. Prominence of the superior aspect of the anterior heart border usually reflects enlargement of the right auricular appendage. In the frontal projection, the right atrial border may appear displaced to the right and cephalad. There may be cephalic displacement of point B (junction of the right atrial border and the vascular arch). The right anterior oblique and left lateral projections are not helpful in evaluation of right atrial enlargement.

Enlargement of both ventricles will displace the apex of the heart caudally and toward the left. However, enlargement of the right ventricle is suspected with convexity of the middle arch of the left heart border. As the right ventricle is not a border-forming structure in the frontal projection, indirect evidence of right ventricular disease is suspected whenever one observes convexity of the middle arch of the left heart border and abnormal pulmonary vascularity. Pulmonary valvular stenosis, left-to-right shunts and pulmonary arterial hy-

pertension are the most common causes of convexity of the middle arch of the left heart border. Rarely, the ascending aorta may occupy the middle arch of the left heart border (in corrected transposition of the great arteries, for example). In some instances abnormal convexity of the middle arch of the left heart border is related to herniation of the left auricular appendage through a partial pericardial defect, or to a non-vascular condition such as an enlarged thymus, or a tumor or adenopathy.

The left lateral projection of the heart provides for the best profile analysis of the right ventricle. Closeness of the anterior heart border to the sternum is not a good sign of right ventricular enlargement, for normally in patients with a narrowed anteroposterior diameter of the chest, the heart is close to or in contact with the sternum. The left and right anterior oblique projections are not informative for the evaluation of right ventricular enlargement.

The best view for evaluating left ventricular enlargement is the left anterior oblique projection. In this view when the left ventricle is enlarged it usually overlaps and may project beyond the thoracic spine. The angle formed between the left ventricle and the left hemidiaphragm may become obtuse. The right anterior oblique projection is not useful for evaluating left ventricular enlargement. In the frontal projection the shape of the left ventricular arch may reflect volume hypertrophy (broad, large arch) and pressure hypertrophy (rounding, short arch).

Pressure hypertrophy of either ventricle may be indiscernible radiographically. Physical findings and electrocardiography are usually more sensitive than conventional roentgenography for the establishment of right or left ventricular hypertrophy. However, volume hypertrophy of either ventricle modifies heart size and configuration and will exaggerate the convexity of these chambers.

Asymmetric enlargement of the ascending aorta may be seen with aortic valvular stenosis (post-stenotic dilatation) and with syphilis. When the aorta becomes dilated and tortuous, the descending aorta may project beyond the middle arch of the left heart border. In such instances, the right superior mediastinum may show a convex density usually caused by a tortuous dilated or displaced innominate artery. Arteriosclerosis dilates and at the same time elongates the thoracic aorta. As the

thoracic aorta has a fixed position at the level of the aortic valve and at the aortic hiatus of the diaphragm, elongation will occur and will displace the aortic arch anteriorly, cephalically, toward the right, and dorsally, beyond the thoracic spine. Analysis of calcification at the level of the thoracic aorta is important. Dissecting hematoma and syphilis (with ascending aorta calcification) cause characteristic findings. Pericardial, coronary artery

and valvular calcification are best analyzed at fluoroscopy. The best view to separate mitral from aortic valvular calcification is the left anterior oblique view. Aortic valvular calcification will project in the center of the heart and will have a cephalocaudal (head-foot) motion. Mitral valvular calcification will project in the posterior third quadrant of the heart and will have a reverse C-shaped motion.

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In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

AGGELER, PAUL MICHAEL, San Francisco. Died 1 September 1969 in San Francisco of cancer of the lung, aged 57. Graduate of University of California Medical School, Berkeley-San Francisco, 1937. Licensed in California in 1937. Doctor Aggeler was a member of the San Francisco Medical Society.

❖

BRAMWELL, HARRY LISLE, Stockton. Died 26 April 1969 in Stockton of coronary heart disease, aged 73. Graduate of University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Doctor Bramwell was a retired member of the San Joaquin County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

❖

CAMPBELL, LEON GEORGE, Pasadena. Died 3 August 1969 in South Laguna, aged 76. Graduate of Washington University School of Medicine, St. Louis, 1922. Licensed in California in 1922. Doctor Campbell was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

❖

CARTER, ASHBY EDDLESTON, North Hollywood. Died 30 August 1969 in Los Angeles, aged 65. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1929. Licensed in California in 1929. Doctor Carter was a member of the Los Angeles County Medical Association.

❖

CHESBRO, ELMER J., Gilroy. Died 1 August 1969 in Gilroy, aged 75. Graduate of Hahnemann Medical College of the Pacific, San Francisco, 1916. Licensed in California in 1916. Doctor Chesbro was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

❖

CLAY, HORACE SAWYER, Pasadena. Died 1 August 1969 in South Laguna Beach, aged 66. Graduate of the College of Osteopathic Physicians and Surgeons, Los An-

geles, 1939. Licensed in California in 1939. M.D. degree from California College of Medicine, 1962. Doctor Clay was a member of the Los Angeles County Medical Association.

❖

COHEN, BERNARD W., Santa Ana. Died 31 July 1969 in Santa Ana of cancer, aged 63. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1936. Licensed in California in 1946. Doctor Cohen was a member of the Orange County Medical Association.

❖

FINE, IRWIN A., Los Angeles. Died 29 August 1969 in Culver City of coronary artery disease, aged 71. Graduate of New York University and Bellevue Hospital Medical College, New York City, 1922. Licensed in California in 1922. Doctor Fine was a member of the Los Angeles County Medical Association.

❖

GRUNKE, ALBERT RAYMOND, San Diego. Died 24 August 1969 in San Diego, age 42. Graduate of St. Louis University School of Medicine, 1953. Licensed in California in 1964. Doctor Grunke was a member of the San Diego County Medical Society.

❖

HALL, HORACE ALVIN, Colton. Died 27 July 1969 in Loma Linda of metastatic carcinoma of the liver, aged 77. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1920. Licensed in California in 1920. Doctor Hall was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

❖

KESSLER, JOSEPH, San Gabriel. Died 22 August 1969 in San Gabriel of subarachnoid hemorrhage, aged 50. Graduate of University of Virginia School of Medicine, Charlottesville, 1943. Licensed in California in 1949. Doctor Kessler was a member of the Los Angeles County Medical Association.

❖

MARTIN, JOHN STEPHEN, San Diego. Died 11 August 1969 in San Diego of heart disease, aged 65. Graduate of University of Illinois College of Medicine, Chicago, 1939. Licensed in California in 1939. Doctor Martin was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

❖

MASTROPAOLO, ANTHONY JOHN, Downey. Died 22 July 1969 in Downey of myocardial infarction, age 59. Graduate of the University of Cincinnati College of Medicine, 1937. Licensed in California in 1956. Doctor Mastro-paolo was a member of the Los Angeles County Medical Association.

MAXWELL, MARK, Orange. Died 9 August 1969 in Orange of heart disease, aged 37. Graduate of Baylor University College of Medicine, Houston, 1962. Licensed in California in 1963. Doctor Maxwell was a member of the Orange County Medical Association.



NASH, RONALD D., Oakland. Died 10 August 1969 in Piedmont of myocardial infarction, aged 53. Graduate of the University of Toronto, 1941. Licensed in California in 1959. Doctor Nash was a member of the Alameda-Contra Costa Medical Association.



NUTTING, RAYMOND JAMES, Piedmont. Died 28 August 1969 in Oakland of carcinoma of the prostate, aged 78. Graduate of University of Michigan Medical School, Ann Arbor, 1917. Licensed in California in 1920. Doctor Nutting was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.



OPPENHEIMER, LEON INGRAHAM, Oakland. Died 22 August 1969 in Oakland, aged 79. Graduate of Rush Medical College, Chicago, 1918. Licensed in California in 1924. Doctor Oppenheimer was a retired member of the Alameda-Contra Costa County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



PERTUIT, CAMILE JOSEPH, Richmond. Died 31 July 1969 in Napa of myocardial infarction, aged 49. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1946. Licensed in California in 1946. Doctor Pertuit was a member of the Alameda-Contra Costa Medical Association.



ROSEN, SAMUEL, Los Angeles. Died 8 August 1969 in Los Angeles of coronary thrombosis, aged 88. Graduate of University of Minnesota Medical School, Minneapolis, 1904. Licensed in California in 1943. Doctor Rosen was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



SCHNEIDER, EDWIN H., Los Angeles. Died 3 June 1969 in Los Angeles of heart disease, aged 83. Graduate of University of Minnesota Medical School, Minneapolis, 1910. Licensed in California in 1912. Doctor Schneider was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

STAILEY, HENRY DAVID, Santa Rosa. Died 23 August 1969 in Santa Rosa, aged 74. Graduate of Jefferson Medical College of Philadelphia, 1930. Licensed in California in 1931. Doctor Stailey was a retired member of the Sonoma County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



SULLIVAN, JOHN J., Oakland. Died 6 August 1969 in Oakland of arteriosclerotic heart disease, aged 69. Graduate of the University of California Medical School, Berkeley-San Francisco, 1929. Licensed in California in 1929. Doctor Sullivan was a member of the Alameda-Contra Costa Medical Association.



WEIL, HANS JOSEPH, Long Beach. Died 17 August 1969 in Long Beach of myocardial infarction, aged 63. Graduate of Johann Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt-am-Main, Prussia, 1930. Licensed in California in 1941. Doctor Weil was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



WHITE, HARRY ALLEN, Los Angeles. Died 13 August 1969 in Los Angeles of heart disease, aged 71. Graduate of New York University and Bellevue Hospital Medical College, 1923. Licensed in California in 1925. Doctor White was a member of the Los Angeles County Medical Association.



WILLSON, WESLEY W., Burbank. Died 5 July 1969 in Burbank, aged 72. Graduate of Detroit College of Medicine and Surgery, 1919. Licensed in California in 1946. Doctor Willson was a member of the Los Angeles County Medical Association.



WOLFRAM, MARTHE C., Oakland. Died 18 August 1969 in Berkeley, aged 71. Graduate of the University of Cincinnati College of Medicine, 1927. Licensed in California in 1929. Doctor Wolfram was a member of the Alameda-Contra Costa Medical Association.



WOODS, DANIEL LINDLEY, Cathedral City. Died 7 August 1969 in Palm Springs of cerebral hemorrhage, aged 71. Graduate of Rush Medical College, Chicago, 1928. Licensed in California in 1928. Doctor Woods was a member of the Los Angeles County Medical Association.

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PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

Current Status of Tuberculin Testing

This statement represents policies accepted by the United States Public Health Service, American Thoracic Society, National Tuberculosis and Respiratory Disease Association, the California Conference of Local Health Officers and the California State Department of Public Health.

CURRENTLY THE BEST diagnostic tool for the identification of persons infected with *M. tuberculosis* is the tuberculin skin test. It should be a part of a routine physical examination and should be included among diagnostic tests for all ill persons.

The test of choice and the accepted test in California is the 5 Tuberculin Unit (0.0001 mg) intradermal tuberculin test using PPD-S (Standard)* which is the most specific antigen for identification of infection with *M. tuberculosis*. PPD-C (Commercial) may be used when PPD-S is not available. The Tine and Heaf tests are screening tests only, and all doubtful reactions should be confirmed with the accepted intradermal tuberculin test. Disadvantages of these tests are that accurate dosage cannot be controlled or measured, and some tests use OT (Old Tuberculin) which is not as specific as PPD-S or PPD-C for identifying infection with *M. tuberculosis*. The 5TU test dose was derived after hundreds of thousands of tests which sought to select a single dose which would yield sensitivity in 95 percent of the infected population. Tests with doses of increasing strength not only are not

practical but have increasing loss of specificity, i.e., stronger doses than 5TU elicit an increasing number of cross reactions, or "false positives" due to infection with atypical mycobacteria.* Cross reactions occur in minimal numbers with the 5TU dose of PPD, and vary with the prevalence and geographic location of atypical infection in the United States, being more prevalent in warm, dry, low altitude areas. Most cross reactions to the 5TU test dose tend to be small and fall in the 5 to 10 mm size range. By contrast, specific reactions to *M. tuberculosis* average around 16 mm in size with a range of 12 to 20 mm for 66 percent of the population and 8 to 24 mm for 95 percent of the population. Specific reactions become fewer and fewer with decreasing reaction size. Therefore, we recognize a size range of 5 to 10 mm where specific and cross reaction sizes overlap which we arbitrarily term as "doubtful," meaning we question whether they are caused by true tuberculous infection, or by some cross-reacting atypical mycobacterial infection. The probability of true tuberculous infection increases with increasing reaction size, and the probability of a cross sensitivity increases with decreasing reaction size.

Comparative Mantoux testing has recently been introduced as a method for distinguishing more precisely between specific and cross reactions. In this procedure, two intradermal tests are given simultaneously, one on each forearm, one test with 5TU of PPD-S tuberculin and the other with a corresponding dose of a PPD-B (Battey) prepared from an atypical Group III (Battey) bacillus. Both tests are read after 48 or 72 hours, as in the standard Mantoux test, by measuring the widest transverse diameter of induration. Results are interpreted according to the comparative sizes of the

*The work of Florence Seibert of the Henry Phipps Institute in Philadelphia in making a better tuberculin culminated in 1934 in the development of Purified Protein Derivative (PPD), a highly potent and stable product without sensitizing properties. One batch, prepared by Seibert in 1939-40, was adopted by the World Health Organization in 1952 as the international standard for mammalian type PPD tuberculin and was designated PPD-S. Dosage is measured in terms of protein nitrogen and expressed in milligrams. PPD-S is currently being made available by the United States Public Health Service through local health departments.

*The human tubercle bacillus is but one of a group of mycobacteria that contains species ranging from saprophytes to obligate parasites. As far back as 1930, it was suspected by some workers that not all reactions to tuberculin could be attributed to tuberculous infection, especially those reactions elicited by large doses of tuberculin. These cross reactions were found to be due to mycobacteria other than tubercle bacilli, and are referred to as atypical mycobacteria. Commonly they are classified by Runyon Groups, i.e., Group I, *M. kansasii* (photochromogens), Group II, Gause (Scotochromogens), Group III, Battey (non-chromogens), and Group IV, Rapid growers. Recently there has been considerable interest in these atypical mycobacteria because it has been found they sometimes cause tuberculous-like disease involving the lungs and lymph nodes.

two reactions.* At the present time, and for most practical purposes, the Public Health Service has made the following recommendations for the interpretation of comparative testing:

1. Where the reaction size to PPD-S is 10 mm or more and PPD-B is any size } positive for tuberculous infection
2. In the doubtful range (5 to 9 mm) where PPD-S is 5 to 9 mm and PPD-B is larger than S } not tuberculous infection
- PPD-B is smaller than S } positive for tuberculous infection
- PPD-B is the same size as S } doubtfully positive for tuberculous infection
3. When PPD-S is less than 5 mm and PPD-S is any size } not tuberculous infection

The identification of persons who are truly infected with *M. tuberculosis* as distinguished from those who are infected with atypical mycobacteria assumes tremendous importance in light of the United States Public Health Service and Navy studies where 625,000 Navy recruits were dually tested with PPD-S and PPD-B (Battey) antigens. Results of this study* revealed that the risk of developing active diseases is directly related to infection with *M. tuberculosis*. Data from this paper, "Identifying the Tuberculous Infected,"† by Palmer and Edwards, graphically demonstrates the risk of development of active disease. In those where reaction size is over 12 mm to PPD-S, the risk of developing active disease is 330 per 100,000 men tested. In those with reactions of 6 to 11 mm to PPD-S where the reaction size to PPD-S is greater than to PPD-B the risk is 298 per 100,000 men tested, stressing the importance of not only identifying positive reactors but also of selecting out those among doubtful reactors who are truly infected with *M. tuberculosis* rather than the atypical

mycobacteria. These persons can then receive INH (isoniazid) preventive treatment for one year. The United States Public Health Service chemoprophylaxis field trials over the past 15 years have shown that preventive treatment for one year reduces the risk of development of active disease by 85 percent in the first year after receiving isoniazid.

Groups which should be tuberculin tested are:*

1. All children between 6 and 12 months of age, whether seen in physicians' offices or child health conferences. When feasible, tuberculin testing should be done before measles immunization and smallpox vaccination; this is not possible in mass immunization programs.
2. Annual tuberculin testing on non-reactors in high risk groups up to the age of 4 years and every two years thereafter, depending upon the risk of exposure and the prevalence of tuberculosis in the population group.
3. Persons receiving a medical workup in the differential diagnosis of any disease.
4. Prior to initiating long-term steroid therapy (longer than a few days) and at three-month intervals, for as long as the patient is on steroids.
5. Three months following infection with measles and whooping cough and again in six months in cases where the status of the tuberculin test was not known prior to infection.
6. School populations — tuberculin testing in order of priority:
 - (a) School enterers; *i.e.*, kindergarten and first grade students, and students new to school in all grades
 - (b) Fourteen-year-olds (age of puberty)
 - (c) Other age levels should be included if the school population is composed of large numbers of high-risk individuals, *i.e.*, poverty and minority groups, farm workers, etc.
7. Other high-risk individuals include positive reactors who are also diabetics, silicotics, pregnant women; persons with gastrectomies, Hodgkins or other reticuloendothelial disease.

It is important to stress again that the frequency with which tuberculin tests should be repeated in pediatric age groups should be related to the inci-

*A large reaction to PPD-B does not necessarily signify infection with Battey, as other atypical mycobacterial infections give cross-reactions to Group III (Battey), Group II Gause (Scotochromogens) and avian tuberculous infections and a lesser degree of cross-sensitivity with Group I (*M. Kansassii*) infection. PPD-B is thus useful as a "broad spectrum" antigen for detecting atypical mycobacterial infection, although the reaction cannot be interpreted as specific or diagnostic for one particular type of atypical infection.

†*Identifying the Tuberculous Infected*, JAMA, Vol. 205, No. 3, July, 1968.

*Joint Committee Statement, Academy of Pediatrics and American College of Chest Physicians, 1 Jan. 1966.

dence and prevalence of tuberculous infection in the population and the risk of exposure to communicable tuberculosis.

We have the following information from the United States Public Health Service for school tuberculin testing programs comparing the United States and California for 1967-68 as follows:

<i>United States</i>	<i>Number Tested</i>	<i>Percent Positive Reactors (10 + mm)</i>
Kindergarten	52,827	0.3%
1st Grade	84,866	0.6%
7th, 8th & 9th Grades	127,708	2.1%

<i>California</i>	<i>Number Tested</i>	<i>Percent Positive Reactors (10 + mm)</i>
Kindergarten	26,311	0.4%
1st Grade	4,102	0.4%
7th, 8th & 9th Grades	11,606	3.0%

With a positive reactor rate of only 0.4 percent among school enterers in California, it becomes apparent that we are approaching a tuberculin negative population of school enterers. Our goal is a tuberculin negative population of 14-year-olds. Finding a positive reactor among school enterers implies that it should be possible to find the source case since most children of this age have an average of only four close contacts.

X-RAY STUDIES IN ESOPHAGEAL DISEASE

"The esophagus is sort of a buried organ. You can't auscultate it; you can't palpate it, and you can't percuss it. So you really must rely very heavily on the radiologist....

"The barium swallow and cineradiography are standard procedures in most hospitals . . .; and in most cases they will outline the abnormality. But if they don't, several other tests can be utilized in any radiology department.

"The first is the water reflux test. Many patients have esophagitis, and a hiatal hernia may be difficult to demonstrate. We have been able to demonstrate reflux by the use of this test. Usually the radiologist will have the patient fill his stomach with barium and then swallow a glass of water. . . . This allows him a double-contrast procedure. With this double contrast, reflux is usually demonstrated brilliantly.

"The so-called marshmallow test . . . is very helpful. Most people who have dysphagia do not have difficulty swallowing liquids; they have difficulty swallowing solids. The radiologist may miss an abnormality if the patient merely swallows liquid barium. A marshmallow dipped in barium is very helpful in outlining the abnormality. This test can be done by any radiologist, cineradiography later demonstrating the dynamic abnormality to the clinician who can then study it. Not only does this test allow one to find the abnormality; but in most cases, it will reproduce pain when the esophagus is distended; and this makes the patient more aware of the abnormality. . . .

"Finally there is the so-called acid barium mixture. I pointed out that acid in the esophagus in the individual with esophagitis may produce heartburn or reduplication of symptoms. By dropping the pH of barium with some hydrochloric acid, one may find a motor disturbance in the lower esophagus and actually a reduplication of symptoms when the acid barium mixture is taken."

—LAWRENCE D. WRUBLE, M.D., Memphis
Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 1, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

CONTINUING EDUCATION

ACTIVITIES

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

- CMA:** California Medical Association
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University
Contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University
Contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5940.
- UCD:** University of California, Davis
Contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0333.
- UCI:** University of California — California College of Medicine, Irvine
Contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA:** University of California, Los Angeles
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
- UCSD:** University of California, San Diego
Contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
- UCSF:** University of California, San Francisco
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

CANCER

November 15-16 — **Fifth Annual Clinical Cancer Conference.** UCSF. Saturday-Sunday. For general practitioners and specialists. Saturday: Tumor and Endocrine Activity, Tumors Sensitive to Changes in Hormonal Environment. Sunday: Cancer Surgery—Problems and Advances. \$50.

December 7 — **California Tumor Tissue Registry — Semi-Annual Cancer Conference.** Beverly Hilton Hotel, Beverly Hills. Sunday 9:00-5:30. Lymphomas and Hodgkin's Disease. Contact: W. K. Bullock, M.D., Exec. Dir., Los Angeles County Hospital, 1200 N. State St., Los Angeles 90033.

December 13 — **Radiotherapy Symposium — Lymphomas & Hodgkin's Disease.** Southern California Permanente Medical Group at Ambassador Hotel, Los Angeles. Saturday, 8:30 a.m.-3:30 p.m. Pathological classifications, medical aspects, and chemotherapy. Contact: Shirley Gach, Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

MEDICINE

November 1-2 — **Coronary Care Symposium.** Orange County Heart Association at Disneyland Hotel, Anaheim. Saturday-Sunday. Contact: Miss Liggett McLaws, Program Director, OCHA, 1043 Civic Center Drive West, Orange 92702. (714) 547-5976.

November 3-12 — **Cardiology for the Consultant — A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. Ten day program for already well-trained consulting clinicians. Enrollment limited to 25. Contact: William D. Nelligan, Exec. Dir., American College of Cardiology, 9650 Rockville Pike, Bethesda, Md., 20014.

November 3-14 — **Coronary Care Unit Program for Physicians.** CRMP, Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly through May, 1970. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitors, placement of pacing catheters, new aspects in diagnosis and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P. H., Administrative Associate, CRMP, Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.

November 5-6 — **Spatial Analysis of EKG.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday. To be followed by six one-session workshops on the first Monday of each month. \$150.

November 5-6 — **Albert M. Snell Memorial Lectures.** Palo Alto Medical Research Foundation at Palo Alto High School Auditorium. Wednesday-Thursday 8:00 p.m. Wednesday: Abdominal Gas. Thursday: Some More Fundamentals of Chest Roentgenology. Contact: Marcus A. Krupp, Director of Research, Palo Alto Medical Research Foundation, 860 Bryant St., Palo Alto. (415) 326-8120.

November 8-9 — **Manipulative Medicine.** USC. Saturday-Sunday. Pathophysiology and treatment of musculoskeletal pain. \$50.

November 13 — **Office Dermatology.** USC. Wednesday 8:30-4:15. Diagnosis and management of skin diseases commonly encountered by the nondermatologist. \$30.

November 13-15—**West Coast Allergy Society.** Hilton Inn, San Diego. Thursday-Saturday. Contact: Betty J. Jones, Exec. Sec., P.O. Box 42067, Portland, Ore. 97242.

November 19—**Clinical Aspects of Asthma.** Tuberculosis and Respiratory Disease Association of Los Angeles County and the Pediatric Respiratory Disease Center of LAC-USC Medical Center. Wednesday 8-5:00. Emergency treatment, early detection and prevention, immunotherapy, steroid treatment, status asthmaticus, emotional problems, and institutionalization. \$25. Contact: Mrs. Rose Schlichter, TBRD Assoc., 1670 Beverly Blvd., Los Angeles 90026. (213) 483-3220.

December 1-12 — **Coronary Care Unit Program for Physicians.** See Nov. 3-14.

December 2-5—**Reticuloendothelial Society—6th Annual Meeting.** Jack Tar Hotel, San Francisco. Tuesday-Friday. Contact: Ernest L. Dobson, Ph.D., General Chairman, Donner Laboratory, University of California, Berkeley 94720.

December 4-6—**Cardiovascular Therapeutics.** American College of Cardiology in cooperation with UCSD, Scripps Clinic and Research Foundation, San Diego County Heart Assoc., and California Heart Assoc. at UCSD. Thursday-Saturday. Thurs., Treatment of Coronary Artery Disease. Fri., Cardiac Pharmacology. Sat., Surgical Treatment of Heart Disease. \$50 for ACC members, \$85 for nonmembers. Contact Eugene Braunwald, M.D., Professor and Chairman, Dept. of Medicine, UCSD.

December 12-14—**Coronary Artery Disease and Cardiovascular Therapeutics.** American College of Cardiology in cooperation with University of Hawaii School of Medicine at Ilikai Hotel, Honolulu. Friday-Sunday. Natural history and anatomy of coronary artery disease, cardiac conduction system, sudden death, newer anti-arrhythmic drugs and adrenal blocking agents, current status of implantable pacemaker, revascularization of myocardium and coronary care monitoring. Contact: William D. Nelligan, Exec. Dir. ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

January 13-14—**The American College of Cardiology—Annual Conference on Clinical Cardiology: New Developments in Diagnosis, Evaluation and Medical and Surgical Aspects of Therapy.** American College of Cardiology in cooperation with UCD and Sacramento Medical Center at Sacramento Medical Center, Sacramento. Tuesday-Wednesday. Designed for generalist, internist and cardiologist. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

January 14—**Seminar on Respiratory Diseases.** Tuberculosis and Respiratory Disease Association of Contra Costa at Holiday Inn, Concord. Wednesday 9-5:00. Didactic sessions and group seminars will cover allergic aspects of respiratory disease in children and adults, infectious respiratory disorders and the spectrum of chronic obstructive lung disease, film on spirometry. Contact: Mitchell Tarkoff, M.D., Chairman, Medical Education Committee, TB and Respiratory Disease Assoc. of Contra Costa, 105 Astrid Drive, Pleasant Hill 94523. (415) 935-0472.

January 16-17—**Modern Trends in Epilepsy: Medical and Sociological Aspects.** UCSF. Friday-Saturday.

January 16-18—**Total Rehabilitation—A Road to Work for "Unemployable" Cardiac Patients.** Ben R. Meyer Rehabilitation Center of Cedars-Sinai Medical Center, Cedars of Lebanon Hospital Division at Sheraton-Universal Hotel, Los Angeles. Thursday-Sunday. Contact: John H. Aldes, M.D., Director, Ben R. Meyer Rehabilitation Center, Cedars of Lebanon Hospital Division, 4833 Fountain Ave., Los Angeles 90029.

January 17—**Workshop in Advanced Arrhythmias.** PMC. Saturday.

January 21—**14th Annual Midwinter Symposium on Cardiovascular Research.** Los Angeles County Heart Association at the Hilton Hotel, Los Angeles. Wednesday. Contact: Joe Kennelley, Director, Public Information LACHA, 2405 West 8th St., Los Angeles 90057. (213) 385-4231.

February 2-3—**Symposium of Arrhythmias.** American College of Cardiology in cooperation with UCI at Newporter Inn, Newport Beach. Sunday-Tuesday. Latest anatomical, pharmacological, and physiological bases for disturbances of cardiac rhythm related to specific disease entities and situations. Workshops will demonstrate clinical application of basic concepts. Contact: UCI.

February 6—**Stroke Symposium.** CRMP, Area VII at Hotel Del Coronado, Coronado. Friday. \$10. Contact: Michael Shimkin, M.D., Director, CRMP, Area VII, 7816 Ivanhoe, La Jolla 92037. (714) 459-3739.

Grand Rounds—Medicine

Tuesdays

9-10:30 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Wednesdays

Grand Rounds in Internal Medicine. 10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

Grand Rounds in Internal Medicine. 12:30-1:30 p.m., University Hospital, UCSD.

Grand Rounds in Internal Medicine. 1:30-3:00 p.m., Fresno General Hospital.

Thursdays

10:30-12:00 noon, Room C3-105, UCLA Medical Center. UCLA.

Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundations.

2-3:00 p.m., Classroom, Third Floor, Fresno General Hospital, Fresno. CRMP Area IV.

Rheumatology Grand Rounds. 11:30 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

OBSTETRICS AND GYNECOLOGY

November 12-16—**Pacific Coast Fertility Society—17th Annual Meeting.** El Mirador Hilton Hotel, Palm Springs. Wednesday-Sunday. For physicians and nurses. Recent developments in reproductive physiology and an infertility workshop. Contact: Gregory Smith, M.D., Exec. Sec., Pacific Coast Fertility Society, 909 Hyde St., San Francisco 94109.

December 6—**Obstetrics & Gynecology.** PMC. Friday-Saturday. 8:30-4:30. New clinical concepts and problems for the family physician and the gynecological surgeon.

PEDIATRICS

November 8-9—**Pediatric Neuroradiology.** UCLA. Saturday-Sunday.

November 10-12—**The Fetus and the Newborn.** American Academy of Pediatrics at UCSF. Monday-Wednesday. Contact: William H. Tooley, M.D., 327 Crestmont Dr., San Francisco 94131. (415) 566-7637.

December 6-7—**Second Annual Children's Hospital Medical Center Symposium.** Memorial Hospital of Long Beach, Long Beach. Saturday-Sunday. Contact: Norman R. Nager, Director of Public Relations, Memorial Hospital of Long Beach, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

February 7—**Pediatric Urology.** UCSF at Childrens Hospital, San Francisco. Saturday.

February 9-20—**Mental Retardation.** UCLA in cooperation with Pacific State Hospital, Pomona at UCLA Neuropsychiatric Institute. Two weeks. For physicians and allied professionals. Causation, symptomatology, care, treatment and management, diagnostic techniques suitable for office practice, parental reactions and intra-family psychopathology, and recent research findings. Contact: UCLA.

Grand Rounds—Pediatrics

Tuesdays

8:30 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Conference Room, Sixth Floor, Harbor General Hospital, Torrance. CRMP Area IV.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and the Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Stanford University Medical Center, Palo Alto.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

PSYCHIATRY

November 1-2—**The Many Faces of Alcoholism.** UCSF at Knotti Harbor Inn, Kelseyville. Saturday-Sunday. Causes, long-term and short-term consequences, treatment, and the significance of the Powell Case. \$15.

November 8—**The Context of Marriage.** UCSF. Saturday.

November 8-9 and 15-16 — **Intermediate Methods in Family Therapy.** UCSF at San Joaquin County Mental Health Services, Stockton. Two weekends. For physicians and allied health professions. Basic theories, methods, and techniques, family therapy session, communication theory, role-playing and psychodrama, and treatment methods. \$25.

November 11-16—**Society for Clinical and Experimental Hypnosis—21st Annual Meeting.** Stanford University, Palo Alto. Tuesday-Sunday. Contact: Mrs. Mario Kenn, Society for Clinical and Experimental Hypnosis, 353 W. 57th St., New York 10019.

November 15—**Modern Theories in Psychiatry.** UCSF at Napa State Hospital, Imola. Saturday 8:45-4:00 p.m. Behavioral Science and Psychiatry, Can Computers Demonstrate Emotional Problems, Intrapsychic Strain and Social Role, Biosocial Psychiatry. \$7.50.

December 6-7 — **Group Therapy and Personality Changes.** UCSF at Mendocino State Hospital, Talma. Saturday-Sunday. Various aspects of group psychotherapy; the marathon group, couples and family groups, psychoanalytic and group psychotherapy. \$15.

December 13-14—**Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton. Saturday-Sunday.

January 7—**Group Methods.** UCSF at V.A. Hospital, San Francisco. Wednesdays 11:30 a.m.-1:00 p.m. through March 11. For physicians and para-professionals in the mental health field. Various aspects of group psychotherapy; personal experience in group process, role playing, group treatment and the generation gap, couples, family, adolescent and marathon groups and color marathon racial confrontation. \$25 full program, \$2 individual lectures.

RADIOLOGY—PATHOLOGY

December 5-7 — **California Society of Pathologists — Annual Winter Meeting.** Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. Presented in conjunction with College of American Pathologists, a Program on Infectious Hospital Diseases and a Seminar on Lymphomas and Hodgkin's Disease presented by the California Tumor Tissue Registry. Contact: L. Miles Snyder, Exec. Sec., California Society of Pathologists, 1831 I St., Sacramento 95814. (916) 443-6744.

January 31-Feb. 1—**Los Angeles Radiological Society—22nd Annual Midwinter Radiological Conference.** International Hotel, Los Angeles. Saturday-Sunday.

Diagnosis, therapy, and nuclear medicine. \$30. Contact: Arthur F. Schanche, M.D., 8618 So. Sepulveda, Suite 100, Los Angeles 90045.

SURGERY—includes Anesthesiology

December 4-6—Diagnosis and Management of Uveitis—Annual Proctor Foundation Program. UCSF. Thursday-Saturday. \$125.

December 12-14—Fluid & Electrolytes. USC at Palm Springs. Friday-Sunday.

December 12-14 — Office Procedures in Orthopedics. UCLA. Friday-Sunday.

January 12-16—Otologic Surgery. Los Angeles Foundation of Otolaryngology and USC in cooperation with St. Vincent's Hospital at St. Vincent's Hospital, Los Angeles. Monday-Friday. One day will be devoted to otosclerosis surgery, three days to surgery of chronic ear disease. One day devoted to inner ear problems, glomus tumors, and facial nerve paralysis. Contact: Glenn Snyder, Managing Director, Los Angeles Foundation of Otolaryngology, 2130 W. Third St., Los Angeles 90057. \$300.

January 19-23—Research Study Club of Los Angeles—39th Annual Mid-Winter Convention in Ophthalmology and Otolaryngology. Statler Hilton Hotel, Los Angeles. Monday-Friday. Contact: Burns C. Steele, M.D., Secretary, Research Study Club of Los Angeles, 1411 W. Olive Ave., Burbank 91506. (213) 846-3614.

January 23-25—Pediatric Anesthesiology—8th Annual Clinical Conference. Childrens Hospital of Los Angeles at Childrens Hospital. Friday-Sunday. Pre-anesthetic evaluation, methods of induction, choice of agent, pharmacology, iatrogenic diseases, and postoperative care. \$75. Contact: Wayne Herbert, M.D., Division of Anesthesiology, Childrens Hospital of Los Angeles, P.O. Box 54700, Los Angeles 90054.

January 26-30—Techniques in Nasal Surgery. UCLA. Monday-Friday.

February 1-4 — Surgical Anatomy. LLU. Sunday-Wednesday. \$100.

February 7 — Surgical Emergencies. PMC. Saturday 8-4:30. Morning session: Monitoring and Management of Shock. Afternoon: Selected and control problems, workshop including case studies and exercises involving blood and gas data, venous pressures.

February 7-8—Surgical Techniques: A Course for the Small Hospital. UCSF at Franklin Hospital, San Francisco. Saturday-Sunday.

Grand Rounds—Surgery

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

9:30 a.m., Neuroradiology, 10:15 Neurology, 11:15 Neurosurgery. Neurology Conference Building 7, V.A. Hospital, Palo Alto. STAN.

Saturdays

8:00 a.m., Auditorium, University Hospital of San Diego County, San Diego. UCSD.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

OF INTEREST TO ALL PHYSICIANS

November 2-5—California Academy of General Practice — 21st Annual Scientific Assembly. Century Plaza Hotel, Los Angeles. Sunday-Wednesday.

November 15—Mayo Alumni Association—45th Annual Meeting. Century-Plaza Hotel, Los Angeles. Saturday. Contact: Office of the 45th Annual Meeting, 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

November 15-16—Sex and the Professional Man. Christian Medical Society at Monte Corona Conference Grounds, Lake Arrowhead. Saturday-Sunday. Contact: Albert Holt, M.D., 4080 Hoking Way, Los Angeles 90027.

November 16—Medical Assistants in Action. San Francisco Medical Assistants Society at Childrens Hospital, San Francisco. Sunday 9-4:30. \$5. Contact: Mrs. Lorraine Rumpler, 210 Monterey Blvd., San Francisco 94131. (415) 648-4555.

December 3 — Postgraduate Assembly—"Virology for the Practicing Physician"—St. Luke's Hospital of Pasadena. At the Huntington-Sheraton Hotel, Pasadena. Wednesday 9-5:00. Contact: W. K. Bullock, M.D., Chairman, 1969 Postgraduate Assembly, 2632 E. Washington Blvd., Pasadena 91107.

December 5-6—Nasal Obstruction. STAN. Friday-Saturday. A 2-day Symposium on Advances in Diagnosis and Treatment. Of special interest to allergists and otolaryngologists. \$50. Contact: Richard L. Goode, M.D., Div. of Otolaryngology, STAN.

January 2-4—Medicine and Law. The American College of Physicians and USC Postgraduate Psychiatry Dept. at USC. Friday-Sunday. Of special interest to physicians in clinical hospital administrative and teaching roles. Broad overview of significant interface between medicine and law, both theoretical and practical. Medical malpractice will not be a major consideration. \$60 for ACC members, \$100 for nonmembers. Contact: Donald N. Nastulin, M.D., Director Postgraduate Psychiatry, USC.

January 8-9—Drug Therapy. UCSF. Friday-Saturday.

January 10-11—Psychiatry for the Practicing Physician. UCSF at Sutter Memorial Hospital, Sacramento. Saturday-Sunday.

January 15-16—New and Old Antibiotics. USC. Thursday-Friday.

January 17 — West Coast Postgraduate Course, San Luis Obispo. CMA and UCI. Saturday: Clinical endocrinology. Contact: CMA.

January 17-18—Mycology: A Review Course. UCSF. Saturday-Sunday.

January 21-April 29—Clinical Psychiatry for Non-Psychiatrists: A Course in Medical Psychotherapy. UCSF. Wednesdays 1-5:00. Open to physicians and

paramedical specialists, enrollment limited to 14. Weekly interviews with psychiatric patients, supported by individual hours of faculty consultation and joint treatment reviews of all patients and seminars. Seminars will cover diagnosis and management of psychiatric emergencies, psychiatric illness in children, testing, and community psychiatry. \$25.

January 25 — **Office Emergencies, A Symposium for Medical Assistants.** UCSF. Sunday.

January 29-30—**Southern Counties Regional Postgraduate Institute.** CMA, STAN, and Southern Counties Medical Societies at El Mirador Hotel, Palm Springs. Thursday-Friday. Thursday a.m.: Acute Injuries of Hand and Face, Acute Cardiac Emergencies and Their Management. Thursday afternoon: The Comatose Patient, Acute Urological Problems. Friday a.m.: Acute Emergencies in the Infant and Child, Shock, Cranial and Spinal Cord Injuries, Acute Pulmonary Problems. Friday afternoon: Symposium on the Multiple Injured Patient.

January 30-Feb. 1 — **Financial, Tax, and Investment Planning.** UCLA. Friday-Sunday.

January 31—**Suicide.** UCSF. Saturday.

February 7-8—**Abuse of Drugs.** UCSF. Saturday-Sunday.

February 9, 10, 11-March 2, 3, 4—**Annual Postgraduate Circuit Courses—Spring Session.** CMA and STAN at Mt. Shasta Community Hospital; Enloe Memorial Hospital, Chico; and Auburn Faith Hospital, Auburn. Topics: Radiotherapy and Cancer Management, Depression — Disease and Symptom, Pathology — Past, Present and Future, and Injuries of the Hand and Face. \$30. Contact: CMA.

February 9-13 — **Course for Physicians in General Practice.** UCSF at Mt. Zion Hospital and Medical Center, San Francisco. Monday-Friday.

February 11-12—**Symposium on Shock.** USC. Wednesday-Thursday.

February 14—**Cardiac Emergencies.** PMC. Saturday.

Therapy of intractable heart failure, modern concepts of shock, and emergencies arising in the infant.

February 14—**Self Expansion II.** UCSF. Saturday.

RADIO-TELEVISION

Medical Radio Conferences. Live from UCSF. Tuesdays, 12:30-1:30. Heard on:

Auburn—KAFI-FM	Los Banos—KLBS-FM
Berkeley—KPFA-B-FM	Mendocino—KMFB-FM
Bishop—KIBS-FM	Salinas—KRSA-FM
Chico—KEWT-FM	Santa Maria—KSMA-FM
Eureka—KRED	Stockton—KSTN-FM
Fresno—KXQR-FM	Susanville—KSUE
King City—KRKC	Tulare—KBOS-FM

Southern California's Medical Television Network. UCLA. Weekly broadcasts, Tuesdays 8:30 a.m. Contact: UCLA Medical Television Network.

November 4—**Fractures in Children.** CRMP, Area VII.

November 11—**Fair Warning (Smoking Hazards).** Boston Medical Reports.

November 18—**The Anemic Patient.** City of Hope National Medical Center.

November 25—**Epidural Anesthesia.** University of Western Ontario.

CONTINUOUSLY

Basic Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

PRINCIPLES AND PRACTICE OF PODIATRY—Frank Weinstein, D.S.C., F.A.C.F.R., Editor. Lea & Febiger, 600 South Washington Square, Philadelphia, Pa. (19106), 1968. 508 pages, \$22.50.

Dr. Weinstein is the author of the chapters on "History of Podiatry"; "Physical Examination of the Lower Extremities"; "Fractures and Dislocation of Foot and Ankle"; "Foot Orthopedics"; "Roentgenology in Podiatry"; and "Forensic Podiatry." He has delegated the chapter on "Systemic Diseases in the Lower Extremities" to E. G. Kreld, M.D., "Neurologic Diseases" to George Monckton, M.D., and "Evaluation of Foot Disabilities" to R. Graham Huckell, M.D. He acknowledges the help of an orthopedic surgeon in the preparation of the chapter on "Physical Diagnosis," a resident in psychiatry in the chapter on "Foot Orthopedics," a general practitioner in the chapter on "Fractures" and a general surgeon in the chapter on "Foot Surgery."

The section on "History of Podiatry" is informative. The designation *podiatry* was first adopted in 1957 to the total exclusion of the word *chiropody*; however, the degree of D.S.C. (Doctor of Surgical Chiropody) continues to be used. There is a National Board of Examiners, and sub-specialties such as foot surgery, foot roentgenology, foot orthopedics and foot dermatology.

The chapter entitled "Dermatology in Podiatry" by Dr. Marvin Steinberg states, "I urge that under no circumstances should x-ray or radium treatment ever be given for warts or any other benign lesion on the human foot." However, Dr. Lewis O'Keen, in chapter 17, "X-ray Therapy in Podiatry," states that plantar warts, inflamed bursae, corns, excessive sweating or unusually odoriferous sweating, ringworm, athlete's foot, eczema and pruritis are all amenable to x-ray therapy. (Most present-day radiologists who do therapy restrict such therapy to malignant lesions.) Generally speaking, the section on dermatology is well done and extremely complete. The section on nails (or onychology) is an extension and is likewise very complete. (I would not ordinarily believe that 34 pages of a textbook could possibly be devoted to this lifeless, horny topic.) Fifty-two afflictions of the nails are listed.

By definition and inference, *podiatry* refers to the *foot*; however, in chapter 9, the author lists fractures and dislocations of the ankle and suggests surgical treatment with open reduction and bone screws. This appears to be above and beyond the podiatrist's field—and above and beyond his usual capability. The author also suggests that dis-

locating the ankle joint and widening of the ankle mortise is not a serious problem and can be handled by a Gibney bootstrapping.

The chapter on "Psychosomatic Disorders" seems somehow redundant in the context of this rather comprehensive text. At the end, there is a rather weak recommendation to seek psychiatric consultation *unless* the podiatrist is thoroughly grounded in psychodynamics.

The chapter on roentgenology is well done, but perhaps tends to oversimplify diagnosis by x-ray. (One may often go back to an x-ray *after* a diagnosis has been confirmed by some other means and be very brilliant on pointing out all of the special points now easily apparent on the film which were missed before.)

Malignant primary tumors or metastatic tumors are rarely found in the foot; however, the chapter on oncology suggests amputation as treatment for osteogenic sarcoma, chondromyxosarcoma, Erving's tumor, fibrosarcoma, multiple myeloma and synovium.

In summary, this book is well-researched and has voluminous bibliographical references at the end of each chapter. My general criticism is that it does not recommend consultation often enough, and implies that the podiatrist may conscientiously do complete examinations of the human body, including laboratory and x-ray studies, in order to treat the foot.

WILLIAM S. MOWREY, M.D.

* * *

HUMAN LABOR AND BIRTH—Second Edition—Harry Oxorn, B.A., M.D., C.M., F.A.C.S., F.R.C.S.(C); Assistant Professor of Obstetrics and Gynecology, McGill University; Obstetrician and Gynecologist-in-Chief, Reddy Memorial Hospital; and William R. Foote, B.A., M.D., C.M., F.A.C.S., F.R.C.O.G., F.R.C.S.(C); Associate Professor of Obstetrics and Gynecology, McGill University. Appleton-Century-Crofts, Division of Meredith Publishing Company, 440 Park Avenue South, New York, N.Y. (10016), 1968. 538 pages, \$8.50 (Paperbound).

The second edition of this excellent student textbook by two Montreal obstetricians was revised four years after its initial appearance by adding some 50 pages of text and a number of new references to original sources. There are two entirely new chapters that present brief discussions of premature labor and prolonged pregnancy. The preface, for some reason, is identical with that of the first edition and thus makes no mention of the revisions that have added bulk without necessarily making the book more useful.

This text describes succinctly in words and illustrates beautifully with correlated drawings on facing pages almost every conceivable aspect of the various mechanisms of normal and abnormal labor. In addition, there are chapters on pelvic and fetal skull anatomy, induction of labor, obstetric trauma, postpartum hemorrhage, obstetric radiography, anesthesia, and concluding remarks about newborn asphyxia, injuries and malformations. The large numbers of excellent illustrations far exceed those available in the usual textbook and are superb guides to instruction on the manikin or with a living subject. This very practical book should be available in every delivery suite and should be freely consulted by every student, intern or resident exposed to the mechanistic aspects of obstetric practice. Many teachers already have found it invaluable.

CHARLES E. McLENNAN, M.D.

* * *

LYMPHOGRAPHY OF THE CERVICAL LYMPHATIC SYSTEM—U. Fisch, Zurich. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 179 pages, \$15.00.

In the period since 1952, when Kinmonth described a simple method of injection of contrast medium directly into the lymphatic vessels of man, lymphography has gradually gained wide acceptance. Introduction of oily contrast media extended the clinical application of lymphography by permitting the visualization of lymph nodes that had been hidden until then in regions farther away from the site of injection, particularly in the retroperitoneal area.

This book stems from the widening role of lymphography in oncology and the probability that lymphography will become an important factor in the staging of malignant tumors.

The book is extremely well organized. A new technique for the visualization of cervical lymphatic system in man with an oily radiopaque material is described in detail. The technique consists of the cannulation of deep retroauricular lymphatics with polyethylene microtubing under the magnification afforded by an operating binocular microscope. A review of the embryology, anatomy, topography and physiology of the cervical lymphatic system is presented which first of all clarifies the nomenclature of the nodal groups and provides a basis for the interpretation of cervical lymphograms. The nodes are divided into four main groups: junctional, jugular, supraclavicular and spinal. The new term "junctional nodes" was necessary from a topographical and functional point of view. Lymphatic patterns in patients with carcinoma of the head and neck regions are described and correlated with histological findings. Emphasis is placed on the observance of non-specific reaction of the cervical nodes in these patients. Functional and morphological changes in cervical lymph flow following surgery (biopsy and radical neck dissection) and conventional and telecobalt irradiation of cervical areas are discussed in detail.

The strength of this book is its clear detailed documentation of technique, anatomy and interpretation of cervical lymphograms. Although cervical lymphography is still in a developmental stage in contrast to the well-established lymphographic method for the examination of the extremities and the retroperitoneal area, this book represents a comprehensive review of the subject.

This book should be of use to all physicians who wish to review and improve their understanding of the cervical lymphatic system.

A. FRANKLIN TURNER, M.D.

CLINICAL HYPNOTHERAPY—David B. Cheek, M.D., and Leslie M. LeCron, B.A. Grune & Stratton, Inc., 381 Park Avenue South, New York City (10016), 1968. 245 pages, \$7.50.

Since Mesmer in the late 18th century at the time of the French Revolution, mankind has alternately conceived of hypnosis as panacea or treacherous tool of the Devil. These ideas have not only been embraced by the public but by professionals as well. Recently psychiatry has taken a more dispassionate view of hypnosis, aware of its uses and difficulties, but also coolly viewing it as an object for investigation. However, opinion regarding hypnosis remains split into various camps. Most physicians, including many psychiatrists, have little knowledge and still less experience with hypnosis. Like politics, it therefore becomes a fertile field for opinions, speculations and accusations.

To disjoin opinion on hypnosis into a trichotomy one must generalize and risk accuracy for understandability. Nonetheless I will pursue this course in the name of Aristotelian clarity. There is an optimistic liberal camp which feels the dangers of hypnosis are exaggerated and that it is a useful therapeutic tool in surgery, medicine and psychiatry. A cautious group believes the dangers of hypnosis need to be emphasized and that very careful consideration be given to choosing hypnotic subjects. Then there is a skeptical group which knows little about hypnosis but in general fears its applications are limited.

The authors of *Clinical Hypnototherapy* belong to the liberal group. Optimism rings like a clarion throughout. David Cheek, M.D., an obstetrician and gynecologist, and Leslie LeCron, B.A., both have extensive experience in the use and teaching of clinical hypnosis. They extol hypnosis as a useful clinical technique in a wide variety of spheres. Their book is an easily understood, well-written course in hypnotic technique and its application. They discuss the use of hypnotic treatment in psychosomatic illness, frigidity, obstetrics, pain, surgery, insomnia, obesity, psychiatry, pediatrics and dentistry. The text is replete with examples of what to say to patients and why. It provides a most interesting, enjoyable and useful exploration for any clinician into the world of hypnotic phenomena.

The authors are psychologically oriented and believe in a dynamic-genetic approach to illness. They feel the "dangers of hypnosis are minimal and can be avoided." Moreover they feel that insight into unconscious determinants of an illness often leads to recovery. They emphasize hypnosis as particularly useful since it can rapidly cut through resistances to the unconscious and therefore achieve insight more quickly.

I believe the authors somewhat overestimate the role of insight in the resolution of illness. Insight is important but a major factor is time. It is with the fabric of time that the patient can achieve a genuine restructuring and re-integration of the ego. It is to be remembered that almost all symptoms of psychiatric origin are evanescent and wax and wane with time. Thus, a true cure rate can only be measured on the basis of an asymptomatic state occurring over a relatively long span of time. Nonetheless, if the optimism and skillful therapeutic technique taught in clinical hypnosis is captured by a clinician, the patient's hope and surge toward growth and recovery may more easily be reached.

JAMES E. HUGHES, M.D.

or here.



). Though generally not recommended, if bination therapy with other psychotropics is indicated, carefully consider individual pharmacologic effects, particularly in use of potating drugs such as MAO inhibitors and nothiazines. Observe usual precautions in enence of impaired renal or hepatic function. idoxical reactions (e.g., excitement, stimula- and acute rage) have been reported in psytric patients. Employ usual precautions in timent of anxiety states with evidence of imding depression; suicidal tendencies may be ent and protective measures necessary. Vari- effects on blood coagulation have been orted very rarely in patients receiving the g and oral anticoagulants; causal relation- has not been established clinically.

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BOOKS RECEIVED

Books received by CALIFORNIA MEDICINE are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.

ANOREXIA NERVOSA — Peter Dally, M.B., F.R.C.P., D.P.M., Physician in Psychological Medicine, Westminster Hospital, London. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 137 pages, \$4.75.

BEDSIDE DIAGNOSTIC EXAMINATION — Second Edition — Elmer L. DeGowin, M.D., Professor of Internal Medicine, University of Iowa College of Medicine, Iowa City; Richard L. DeGowin, M.D., Associate Professor of Internal Medicine, University of Iowa College of Medicine, Iowa City. The Macmillan Company, 866 Third Avenue, New York City 10022. 923 pages, \$9.95.

A DICTIONARY OF DERMATOLOGICAL WORDS, TERMS AND PHRASES — Morris Leider, A.B., M.D., Associate Professor of Dermatology, New York University School of Medicine, and Morris Rosenblum, Ph.D., Lecturer, Classical Languages and Comparative Literature, The City College of the City University of New York; and formerly Associate, Department of Greek and Latin, Columbia University. McGraw-Hill Book Company (The Blakiston Division), 330 West 42nd Street, New York, N. Y. (10036), 1948. 440 pages, \$10.95.

DIET MANUAL — Second Edition — Compiled by the Dietary Staff of Vanderbilt University Hospital. Vanderbilt University Press, Nashville, Tenn. (37203), 1969. 158 pages, \$6.95.

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DISEASES OF THE CHEST — Third Edition — H. Corwin Hinshaw, M.D., Ph.D., D.Sc., Clinical Professor of Medicine, University of California, School of Medicine, San Francisco; Director of Medical Services, Harkness Community Hospital and Medical Center, San Francisco. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969; 799 pages, 691 illustrations on 294 Figures, \$25.00.

THE HYPERTENSIVE VASCULAR CRISIS — An Experimental Study — F. B. Byrom, M.D., (London) F.R.C.P. London F.R.A.C.P. (Member of the External Scientific Staff of the Medical Research Council). Grune & Stratton, Inc., 381 Park Avenue South, New York, N. Y. (10016), 1969. 131 pages, \$4.75.

I'M DONE CRYING — Louanne Ferris as told to Beth Day. M. Evans and Company, Inc., 216 East 49th Street, New York, N. Y. (10017), and Distributed in Association with J. B. Lippincott Company, New York, 1969. 275 pages, \$5.95.

THE KNOW-HOW OF INFANT FEEDING — Second Edition — Sylvia Close, S.A.N.C. Med. and Surg. (Hons.), S.A.N.C. Midwifery (Hons.), Athlone Mothercraft Certificate. Baby Care Adviser to the National Childbirth Trust. John Wright and Sons Ltd., Bristol, 1969; The Williams & Wilkins Co., Baltimore, Md. 21202, exclusive U.S. agents; 40 pages, \$4.00.

MANUAL ON ARTIFICIAL ORGANS — Volume I — The Artificial Kidney — A Guide to Understanding for the Physician and for the Patient. Yukihiko Nose, M.D., Ph.D., Head, Artificial Organs Research Laboratory, Research Division; Staff, The Cleveland Clinic Foundation, Cleveland. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1969. 343 pages, with 401 illustration, \$27.75.

MEDICAL LABORATORY TECHNOLOGY AND CLINICAL PATHOLOGY — Second Edition — Matthew J. Lynch, M.D. (N.U.I.), F.R.C.P.(C), F.C.Path., F.C.A.P., M.R.C.P. (Lond.), Associate Pathologist, The Hospital for Sick Children, Toronto, Ontario; Assistant Professor, Department of Pathology, University of Toronto; Stanley S. Raphael, M.B., (Lond.), F.R.C.P.(C), F.C. Path., Pathologist Hotel-Dieu Hospital, Windsor, Ontario; Leslie D. Mellor, L.C.S.L.T., F.I.M.L.T., Department of Biochemistry, Women's College Hospital, Toronto, Ontario; Peter D. Spare, F.I.M.L.T., M.R.S.H., A.C.I.C., Clinical Chemist, McKellar General Hospital, Fort William, Ontario; and Martin J. H. Inwood, B. Sc., L.C.S.L.T., F.I.M.L.T., Formerly Chief Technologist, Departments of Hematology and Blood Transfusion, The General Hospital, Sudbury, Ontario, Canada; Undergraduate Student, Faculty of Medicine, University of Western Ontario, London, Ontario. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 1359 pages, \$23.00.

MOMENTS WITH DIAGNOSTIC RADIOLOGY — Vol. 1, The Abdomen — Max J. Ryan, F.F.R., F.F.R.C.S. Irel., D.M.R.D., Radiologist, St. Laurence's (Richmond) Hospital and The Charitable Infirmary, Jervis Street, Dublin; Consultant Radiologist, Royal Victoria Eye & Ear Hospital, Dublin; Consultant Neuroradiologist, Dublin Federated Hospital, and Lecturer in Radiology and Examiner in Fellowship of Faculty of Radiology, Royal College of Surgeons in Ireland. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 116 pages, \$2.75 (Soft cover).

NEUROBIOLOGICAL ASPECTS OF PSYCHOPATHOLOGY — The Proceedings of the Fifty-Eighth Annual Meeting of the American Psychopathological Association, held in New York City, February, 1968 — Compiled and Edited by Joseph Zubin, Ph.D., Department of Mental Hygiene, State of New York; Department of Psychology, Columbia University, New York City; and Charles Shagass, M.D., Eastern Pennsylvania Psychiatric Institute, Philadelphia, Pennsylvania. Grune & Stratton, Inc., 381 Park Avenue South, New York, N. Y. (10016), 1969. 429 pages, \$18.75.

OBESITY AND ITS MANAGEMENT — Benis Craddock, M.D., M.R.C.G.P., D.R.C.O.G., General Practitioner, South Croydon. Foreword by John H. Hunt, M.A., D.M., F.R.C.P., F.R.C.S., President of the Royal College of General Practitioners. Williams & Wilkins Co., 428 E. Preston Street, Baltimore, Md. (21202) (exclusive U.S. agents), 1969. 191 pages, \$8.25.

PATHOGENESIS OF CORONARY ARTERY DISEASE — Meyer Friedman, M.D., Director, Harold Brunn Institute, Mount Zion Hospital and Medical Center, San Francisco, California. McGraw-Hill Book Company (The Blakiston Division), 330 West 42nd Street, New York, N. Y. (10036), 1969. 269 pages, \$19.50.

PHARMACOLOGY AND THERAPEUTICS — Fourth Edition — Ruth D. Musser, A.B., M.S., Assistant Professor of Pharmacology, Retired, School of Medicine, and formerly Chairman of Pharmacology, School of Nursing, University of Maryland, Baltimore and John J. O'Neill, Ph.D., Associate Professor of Cell Biology and Pharmacology, School of Medicine, University of Maryland, Baltimore and other contributors. The Macmillan Company, 866 Third Avenue, New York City 10022, 1033 pages, \$10.95.

RADIOACTIVE ISOTOPES IN THE LOCALIZATION OF TUMOURS — The Proceedings Of The International Nuclear Medicine Symposium Arranged By The Institute Of Cancer Research: Royal Cancer Hospital And Held At The Imperial College Of Science And Technology, London, In September, 1967 — Edited by V. R. McCready, D. M. Taylor, N. G. Trotter, C. B. Cameron, E. O. Field, Rosemary J. French, R. P. Parker. Grune & Stratton, Inc., 381 Park Avenue South, New York, N. Y. (10016), 1969. 180 pages, \$11.75.

REMOVABLE INTRACRANIAL TUMOURS — Leslie Oliver, M.B., B.S., F.R.C.S., F.A.C.S., Consultant Neurosurgeon, Charing Cross Hospital, Westminster Hospital, Royal Northern Hospital, West End Hospital for Neurology & Neurosurgery, West London Hospital, & Senior Consultant Neurosurgeon, North-East Metropolitan Regional Neurosurgical Centre, Oldchurch Hospital, Romford. Grune & Stratton, Inc., 381 Park Avenue South, New York, N. Y. (10016), 1969. 168 pages, \$7.75.

THE RORSCHACH SYSTEMS — John E. Exner, Jr., Ph.D., Director of Training in Clinical Psychology, Long University, Brooklyn, N. Y.; Formerly Director of Training in Clinical Psychology, Bowling Green State University, Bowling Green, Ohio. Grune & Stratton, Inc., 381 Park Avenue South, N. Y. (10016), 1969. 381 pages, \$14.75.

SLEEP — Psychology & Pathology — A Symposium — Edited by Anthony Kales, M.D., Director, Sleep Research and Treatment Facility, Associate Professor, Department of Psychiatry and Brain Research Institute, University of California School of Medicine, Los Angeles. J. B. Lippincott Company, East Washington Square, Philadelphia, Pa. 19105, 360 pages, \$14.00.

A SYNOPSIS OF CONTEMPORARY PSYCHIATRY — George A. Ulett, B.A., M.S., M.D., Ph.D. Professor and Chairman, Department of Psychiatry at the Missouri Institute of Psychiatry (St. Louis), University of Missouri School of Medicine; Visiting Professor of Psychiatry, University of Istanbul, Istanbul, Turkey; Director, Division of Mental Diseases for the State of Missouri, Jefferson City; D. Wells Goodrich, M.D., Professor of Psychiatry, Montefiore Hospital and Albert Einstein College of Medicine, New York City — Fourth Edition — The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Missouri 63103; 1969. 340 pages, \$9.50.



The Management of Abdominal Injuries In the Presence of Head Injury

CHARLES B. WILSON, M.D., *San Francisco*

■ *When head and blunt abdominal injuries are combined, the head injury is often afforded too much attention and the abdominal injury too little, especially when the patient is unconscious. If mismanaged, the abdominal injury is often the more serious threat to life. Except for extradural hemorrhage, neurosurgical intervention, when indicated, can be delayed until the patient has been thoroughly evaluated for the presence of extra cranial injuries with higher therapeutic priority.*

Abdominal examination of the unconscious or uncooperative patient is difficult. Tenderness as a sign of abdominal injury cannot be elicited. Abdominal rigidity (in the absence of rigid extremities), a silent abdomen, shock, and extreme restlessness may indicate intra-abdominal changes. Abdominal paracentesis is a valuable diagnostic aid, and the finding of blood, bile-stained fluid, intestinal contents or air is an indication for immediate laparotomy. Once all injuries are known, priorities for treatment can be assigned. Often head and abdominal injuries can be treated concomitantly.

IN THE PRESENCE of combined head and abdominal injury some neurosurgeons as well as general surgeons tend to ignore the intra-abdominal trauma—the neurosurgeon because of his preoccupation with the head injury and the general surgeon because of his reluctance to carry out the usual

and appropriate measures on an unconscious patient. The sins of both reflect a variable combination of misconceptions. Failure to recognize an intrinsically fatal injury is of less consequence than failure to recognize an injury that is fatal only because it is undetected or is not detected until it is at an irreversible stage.

The following remarks are directed to the general surgeon confronted by a patient with a head injury and known or suspected abdominal trauma.

From the Division of Neurological Surgery, University of California San Francisco Medical Center, San Francisco.

Submitted 28 May 1969.

Reprint requests to: Division of Neurological Surgery, University of California San Francisco Medical Center, San Francisco, Ca. 94122.

Recognition of abdominal injury concomitant with major head injury presents a problem since the usual criteria of intra-abdominal injury are masked.

Diagnosis: Head Injury

We can generally assume that the patient with visible evidence of head trauma probably has some degree of injury to the intracranial contents. If there is any historical, external, or x-ray evidence of trauma to the head, a patient must be managed as having a potentially serious head injury. This policy can do no harm, but to assume that a head injury is inconsequential simply because the patient was unconscious only briefly or not at all may be a serious error in judgment.

Unconsciousness is not tantamount to head injury; one cannot be equated with the other. Full consciousness depends upon simultaneous function of the cerebral cortex and the brain-stem reticular activating system. Loss of function in either system, whether due to hypoxia or mechanical injury, will lead to loss of consciousness. For example, the unresponsive patient with a scalp laceration may be unconscious because of asphyxia from airway obstruction or because of cerebral circulatory failure secondary to systemic hypovolemia.

A brief and systematic neurological examination may confirm suspicion of a head injury but abnormal neurological findings do not provide conclusive evidence of intracranial injuries. For example, major disturbances of motor function may follow injury only to the spinal cord or to more peripheral portions of the nervous system such as the brachial plexus.

Lumbar puncture can be omitted from this discussion, as it has no place in the diagnosis and treatment of acute head injury.

In the patient with known or suspected head injury, plain skull films should be taken but only after any necessary emergency treatment has been given. The value of radiographic examination is limited, but certain findings may be of great importance. Properly positioned films permit recognition of pineal shift, fracture into air-containing paranasal sinuses, fractures across the middle meningeal groove or a major venous sinus, the presence and extent of depressed fractures, and compound fractures not detected by physical examination. In addition, every unconscious patient should have anteroposterior and lateral x-ray studies of the cervical spine. Otherwise, cervical fractures may go

undetected that may cause damage or add to injury already done to the spinal cord.

Diagnosis: The Abdominal Injury

In 1965, in collaboration with general surgical colleagues, I reported a study of 363 patients with blunt abdominal injury, one-fourth of whom also had head injuries.¹ Eleven patients died of unsuspected abdominal injuries; six of the 11 had a concomitant head injury. This experience indicated preoccupation with the head injury, misinterpretation of clinical signs, and insufficient attention to the abdomen. The mortality rate in patients with blunt abdominal trauma was four times greater when associated head injury was present, due in part to the confusion that head injury superimposes on the usual signs indicative of serious intra-abdominal trauma. From this experience emerged certain clinical precepts which bear repetition.

Tenderness cannot be elicited on abdominal examination of a comatose patient, and there may be equal difficulty in evaluating the patient with post-concussion confusion and somnolence. Deprived of the diagnostic information afforded by abdominal examination in a cooperative subject, the surgeon must rely on other evidence of intra-abdominal injury.

Abdominal rigidity cannot be ascribed to head injury unless rigidity is also present in the extremities.² If the extremities are flaccid or have normal muscle tone, a rigid abdomen connotes intra-abdominal injury. A head injury, no matter how serious, can cause neither abdominal rigidity alone, nor ileus. A silent abdomen following combined head and abdominal injury indicates either intra-abdominal injury or injury to the spine. Spinal cord transection causes prolonged paralytic ileus, and thoracic and lumbar vertebral fractures may produce ileus in the absence of injury to the spinal cord. Even in this situation the likelihood of associated intra-abdominal injury cannot be dismissed.

Misconceptions are slow to die and none has been more tenacious than the imaginary entity of central shock. Except as a terminal event, a head injury does not produce shock, and the finding of shock almost certainly indicates major injury elsewhere in the body.^{3,4,7} To quote Meacham, "allowing oligemic shock to remain undisturbed and untreated while waiting for the nervous system to 'readjust' itself, perhaps feebly aided by the solicitous administration of vasoconstrictor drugs, is dangerous, and an error compounded by a reluc-

tance to administer appropriate intravenous fluids to the brain injured patient."⁵

Not often is extreme restlessness seen following brain injury.^{6,7} The patient with recent head injury is characteristically quiet and, in the absence of extracranial complications, prefers to sleep and be let alone. The appearance of restlessness demands immediate evaluation. It is most often caused by cerebral anoxia secondary to hypoxemia or hypovolemia, and second in frequency as a cause is pain due to over-distension of the bladder, unrecognized fractures, or extensive soft-tissue injuries. An uncommon but important cause of restlessness is the severe unilateral headache produced by extradural hematomas.

An earlier study indicated the safety and high diagnostic accuracy of abdominal paracentesis.¹ The finding of blood, bile-stained fluid, air or intestinal contents were an absolute indication for laparotomy. The type of needle used and whether peritoneal irrigation was done were much less important than the proper interpretation of a "negative" tap: the study referred to emphasized the limitations of a single negative tap, the value of repeated taps when indicated by clinical suspicion, and finally the mandatory requirement for laparotomy in spite of negative taps when clinical judgment called for laparotomy. In this last situation, a large retroperitoneal hematoma secondary to renal or skeletal injury often was found at operation. These facts strongly support a policy of routine peritoneal paracentesis in all patients with combined abdominal and major head injuries.

Management of Combined Injuries And Determination of Therapeutic Priorities

A thorough and systematic physical examination is a basic requirement for the management of a patient with serious head injury, and even in an unconscious patient the general examination should precede the neurological examination.⁸ Vital signs will approximate normal values in cases of uncomplicated head injuries. Although a rapid rise in intracranial pressure produces bradycardia, a rising systolic blood pressure and slowing respiratory rate, in that order, a deviation of vital signs from the normal range is due much more often to extracerebral causes. Vital signs will also be disturbed in a patient with primary or secondary brain-stem injury with its associated decerebrate rigidity,

tachycardia, hyperventilation and hyperthermia. With these exceptions a deviation of vital signs from normal values implicates extracerebral factors.

Management of major head injuries involves the care of unconscious patients. In an effort to avoid the aspiration of vomitus, a nasogastric tube is inserted soon after the patient is admitted. The flat, supine position is best for examination but should not be long continued because of the risk of aspiration. The patient should be maintained in a semi-lateral or semiprone position, with position changes from side to side at hourly intervals. In the absence of pulmonary complications and shock, the head is best kept elevated 20° to 30° to encourage venous return from the head. In this regard, the Trendelenburg position does not improve cerebral blood flow in a hypotensive patient, and venous congestion in the head-down position is clearly deleterious.

While over-hydration should be avoided, intravenous fluids need not be restricted because of head injury. In the absence of extraneous fluid loss, 2,000 ml of one-fourth or one-half normal saline solution per day should be administered intravenously. As a rule of thumb, intravenous fluid should provide a daily urinary output of about 1,000 ml. A patient with injury to the head retains salt and water for at least a few days after injury, and the slightly greater water retention produces mild hyponatremia.⁹ In addition, because of an expanded extracellular volume, sodium excretion may be relatively large. The management of fluids in a patient with an uncomplicated head injury poses no problem. In replacing extra-renal fluid loss, the surgeon should take into account the usual metabolic response to head injury.

Neurosurgical indications will be mentioned only briefly.^{7,8} The one true neurosurgical emergency is extradural hemorrhage. The typical patient has minor trauma to one temple, followed by a lucid interval of one to six hours, and then manifests signs of rapidly progressive compression of one cerebral hemisphere. This situation, and none other, is an indication for immediate neurosurgical intervention on suspicion. The emergency treatment of open head wounds is limited to the application of a sterile dressing with no attempt made to remove clotted blood or exposed brain. Definitive debridement can be delayed up to 24 to 48 hours without a significantly increased risk of infection, provided prophylactic antibiotic therapy is started promptly. Depressed skull fractures with

an intact scalp are treated as closed-head injuries. Almost all depressed fractures should be corrected surgically but they rarely constitute an emergency. Deterioration of neurological function demands investigation by either carotid angiography¹⁰ or bur hole inspection. The rate of deterioration determines the degree of emergency and the appropriate actions.

Among the intra-abdominal injuries, active intra-abdominal bleeding constitutes an immediate threat to life and surgical management is second in urgency only to extradural hemorrhage. Rupture of a hollow viscus is likewise an urgent situation, only slightly less compelling than active intra-abdominal bleeding.⁷

Unless the patient with intra-abdominal injury is in a terminal state from the associated head injury, laparotomy may be undertaken without delay. If there is a concomitant neurosurgical injury requiring operative management, judgment will dictate whether the two operations can proceed simultaneously or the cranial operation should be delayed. In general, unless the intracranial procedure would require several hours of operating time, the two can be done simultaneously once the patient's respiratory status and blood volume are returned to normal.

From what has been stated earlier, head injury does not constitute a contraindication to laparotomy, but rather dictates modification of the procedure customarily followed. An endotracheal tube should be in place during the laparotomy, and a short-acting anesthetic supplemented with muscle relaxants rather than deeper anesthesia should be used to obtain necessary operating conditions. Long-acting agents for pre-medication should be avoided and every effort should be made to begin and terminate the anesthesia quickly.

Conclusions

Meacham has stated that timely tracheostomy or blood transfusion has saved more lives in cases of head injury than all the other methods of supportive therapy combined, including exploratory bur holes for presumed hematoma. Emergency neurosurgical intervention is rarely a life-saving measure in patients with head injuries. By contrast, prompt surgical intervention for traumatic intra-abdominal bleeding saves many lives where both kinds of injury exist. The non-surgical management of head injuries follows fairly simple rules if one can separate misconception from fact. The general surgeon finds himself at a major disadvantage in evaluating the abdomen in the head-injured patient and in this regard abdominal paracentesis assumes a role of great importance. Because unrecognized intra-abdominal bleeding is a significant cause of death among patients with combined head and abdominal injuries, the general surgeon must adopt a more aggressive position in the handling of this common combination.

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The Management of Diabetic Coma

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DIABETIC COMA PRESENTS a medical emergency the outcome of which depends entirely upon prompt and knowledgeable medical attention. The mortality from diabetic coma at certain centers has exceeded 25 percent, while at other centers it is less than 2 percent.¹ We recently reported the treatment of 23 consecutive patients with no mortality.²

Evidence to indicate that mortality can be sharply reduced when an aggressive approach is adopted is provided by the classic report from the Massachusetts General Hospital in which mortality abruptly fell from 20 percent to 2 percent when a new routine of therapy was instituted.³

In recent years the pathophysiology of diabetic coma has been more precisely defined and has provided the foundation for a more rational management. The fundamental derangement is a relative or absolute deficiency of active insulin. The secondary derangements can be explained by the known effects of insulin.

The membrane of cells of the renal tubules and the cells of the central nervous system are permeable to glucose in the absence of insulin. Muscle cell and fat cell membranes, however, are relatively impermeable until a sufficient concentration of circulating insulin acts upon them to allow glucose entry. In addition to its effect on membranes, insulin also brings about a modification in the way the liver manufactures glucose. With insulin deficiency, large quantities of glucose are produced by the liver and released into the circulation. Excessive glucose production and decreased cellular utilization combine to bring about increasing concentrations of glucose in the blood and extracellular fluid.

Such concentrations of glucose result in an osmotic gradient between the interior of the cells and the extracellular fluid which draws water and intracellular electrolytes into the extracellular fluid. The concentration of glucose in the glomerular filtrate is approximately the same as that of the blood. The osmotic diuresis which results carries large quantities of water and extracellular and intracellular electrolytes away in the urine. If hydration and renal function are maintained, the concentration of glucose in the blood rarely rises above 500 mg per 100 ml, since the renal loss of glucose serves to limit the degree of hyperglycemia. As renal function deteriorates, greater quantities of glucose accumulate in the blood.

The average adult presenting in diabetic coma has lost approximately six liters of water, 600 mEq of sodium, 400 mEq of chloride, 400 mEq of potassium, 400 mEq of bicarbonate, and 100 mM of phosphorous.⁴

Even in the absence of ketoacidosis, the dehydration and electrolyte imbalance brought about by extreme hyperglycemia can cause disturbed states of consciousness, progressing to profound coma. This condition has been termed hyperosmotic non-ketotic diabetic coma, and has been observed with increasing frequency since its description by Sament and Schwartz in 1957.⁵ The blood glucose concentration in such cases generally ranges between 600 and 2,000 mg per 100 ml. Most patients with this form of diabetic coma are in the older age group and are found to have mild diabetes after the intense hyperglycemia has been successfully treated.

The reason such extreme hyperglycemia is not accompanied by ketosis is not clear, but recent evidence has been obtained to suggest that it may be the result of an ability to produce just enough insulin to suppress fat mobilization but not enough to promote adequate glucose utilization.⁶

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Insulin acts to suppress fat mobilization in two important ways. Fat in fat cells is present in the form of neutral fat which is a combination of one glycerol molecule with three long, fatty acid molecules. When this combination breaks, both the glycerol and fatty acids are released into the circulating blood. Once the break has occurred, the original glycerol molecule cannot recombine with the fatty acids, but a newly generated molecule of phosphated glycerol can take its place and fix the fatty acids within the cell before they escape into the blood.

Phosphated glycerol is one of the metabolic products of glucose which gains entrance to the cell through the action of insulin. When insulin is deficient, there is an insufficient production of phosphated glycerol to bind up liberated fatty acids.

Insulin acts in a second way to suppress fat mobilization through a direct inhibition of the reaction that produces the breaking off of fatty acids from glycerol. This inhibition may demand a smaller concentration of insulin than the indirect inhibition which results when insufficient quantities of phosphated glycerol are produced.

When free fatty acids are lost from the fat cells, they are carried to the liver, where they are degraded to the short chain acids beta-hydroxybutyric acid and acetoacetic acid. These two organic acids, along with the equilibrium product acetone, make up the "ketone bodies" of the plasma. The acids are highly dissociated in body fluids and readily produce excessive quantities of free hydrogen ions.

Hydrogen ions combine with bicarbonate ions to produce CO_2 and water. Both the increased concentration of CO_2 dissolved in the plasma and the increased content of hydrogen ion act on the respiratory center to produce the increased depth and rate of respiration characteristic of diabetic ketoacidosis (Kussmaul respiration).

The diagnosis of diabetic coma is suggested by the clinical state and supported if glucose or ketone is found in the urine. The diagnosis is confirmed, however, only when abnormal concentrations of glucose or ketone are found in the blood. Many comatose patients who are not in diabetic coma may have glucose or ketone in their urine.

Because of the importance of beginning treatment promptly, the diagnosis cannot be delayed while specimens are sent to the laboratory, nor can treatment be guided by determinations from

the laboratory because there is no time to wait for them.

It is, therefore, important that the diagnosis be made and subsequent management guided by simple bedside laboratory tests in combination with the clinical findings. Fortunately such tests are available. The blood glucose concentration can be estimated with glucose oxidase strips and the plasma ketones can be estimated with nitroprusside tablets.

Several milliliters of blood should be drawn into a heparinized tube. The specimen is divided into two parts and one is briefly centrifuged. A drop of the uncentrifuged specimen is applied to a glucose oxidase test strip (Dextrostix®, Ames). If the concentration is greater than 250 mg per 100 ml, which is the highest concentration registered with Dextrostix, subsequent serial dilutions with saline solution should be made to estimate the magnitude of the blood glucose concentration. A strongly positive reaction with one part blood to two parts of saline solution provides strong supportive evidence for a diagnosis of diabetic coma, even if ketones are absent.

One drop of plasma from the centrifuged portion of the specimen is placed on a nitroprusside impregnated tablet (Acetest®, Ames). In diabetic ketoacidosis, the tablet will turn dark purple within two minutes. If such a reaction occurs, it can be assumed that the blood acetoacetic acid content is greater than 30 mg per 100 ml, which in our experience occurs only in diabetic ketoacidosis.

All normal persons have varying concentrations of acetoacetic acid in their plasma at all times, and in certain circumstances, such as simple starvation, the concentration may be greatly increased. Such levels, however, do not reach those found in diabetic ketoacidosis. The use of intact nitroprusside tablets provides a test which is desirably insensitive and will separate diabetic ketoacidosis from all other forms of ketoacidosis. Not to be used for this purpose are crushed nitroprusside tablets or nitroprusside powder or test paper, as these give a more sensitive test which may be misleading. We have seen nitroprusside tablets over which an oxidation crust has formed, so that they do not readily detect the presence of acetoacetic acid in the serum. If this is suspected, the flat surface of the tablet should be rubbed on a coarse paper towel before the serum is applied.

With the great mobilization of fat which occurs in diabetic ketoacidosis, the serum may at times

be so lipemic that the color of the nitroprusside tablet cannot be properly observed. If this occurs, a drop of the lipemic plasma should be placed on the Acetest tablet and after two minutes should be scraped or blotted off so that the color can be observed. The test is still valid in these circumstances.

If a strongly positive test on the intact tablet is found, it is not necessary to make serial dilutions of the serum before treatment is started, but the plasma should be saved so that this may be done at a later time when comparison with subsequently drawn specimens will provide an index of the efficacy of treatment. A part of the original blood specimen or plasma should be sent to the laboratory for quantitative determination of glucose, urea and electrolytes.

As soon as the diagnosis of diabetic coma is established, an intravenous infusion with an 18-gauge needle should be started. The initial dose of unmodified (crystalline-zinc) insulin should be injected intravenously at that time.

In determining the dose of insulin to be administered, one should not be governed by considerations of how little insulin might be given to obtain desired effects but rather how much insulin may be administered without danger. Patients with ketoacidosis are very resistant to insulin. Statistically, the mortality rate for patients receiving smaller initial doses of insulin is significantly higher than for those receiving larger doses.⁷ Although it was originally felt that patients with hyperosmotic non-ketotic diabetic coma might be successfully managed with smaller doses of insulin, additional experience has indicated that survival is increased when quantities of insulin similar to those used in ketoacidosis are employed.⁸

If the patient has cloudy sensorium, and the blood glucose is 250 mg per 100 ml or greater and the plasma or serum is strongly positive for acetone, we initiate therapy with 200 units of regular insulin intravenously. If the blood glucose is estimated to be over 750 mg per 100 ml by the glucose oxidase test, we use a similar dose of insulin even though the reaction for serum acetoacetic acid is not strongly positive, or is even absent.

We strongly recommend that all insulin be given intravenously, not only to obtain the most rapid effect from the dose administered but because there is less tendency for a prolonged insulin effect extending to a time when it might be undesirable.

The action of subcutaneously administered insulin may persist for six hours or longer.

Only after the initial dose of insulin has been administered and the infusion of intravenous fluids initiated is the serial dilution of plasma necessary for a more accurate estimation of the acetoacetic acid concentration. Blood specimens are drawn at intervals of approximately one hour and subjected to such determinations. The second dose of insulin should be given only after the concentration of glucose and acetoacetic acid in the blood specimen obtained after one hour has been compared with that in the first specimen.

If the concentration of blood glucose (non-ketotic hyperosmotic coma) or serum acetoacetic acid (ketoacidotic coma) has not fallen, or if it is greater than it was initially, another large dose of insulin is injected intravenously. This second dose should be of the same order of magnitude as the first. If, on the other hand, the concentration of blood glucose or serum acetoacetic acid is found to be less than it was initially, a dose of insulin approximately half that of the first one should be given.

In the therapy of ketoacidosis, insulin dosage is based primarily on the concentration of plasma acetoacetic acid. Any time the concentration of acetoacetic acid is found to be less than that obtained an hour before, the dose of insulin injected is approximately half the one preceding. If, however, the concentration of acetoacetic acid is not significantly different from that in the preceding sample, the dose of insulin is either the same as or greater than the one before. If at any time the concentration of acetoacetic acid is found to be increasing, the dose of insulin should be doubled each hour until this trend is reversed. Occasional cases of insulin resistance will be encountered in which thousands of units of insulin are necessary to produce a decrease in the concentration of acetoacetic acid.

Frequently the blood glucose level will fall below 200 mg per 100 ml before acetoacetic acid has disappeared from the plasma. When this occurs, insulin should be continued and hypoglycemia prevented by the infusion of glucose-containing solutions.

In the therapy of non-ketotic hyperosmotic diabetic coma, whenever the blood glucose is estimated to be significantly less than that of an hour before, the dose of insulin should be approximately half of the preceding dose. If the blood glucose

concentration is not less, however, the same dose should be repeated or a larger dose given. Generally, hourly doses in the range of 100 to 200 units are continued until blood glucose falls below 500 mg per 100 ml.

It must be borne in mind that although the patient in diabetic coma has lost large quantities of sodium, he has lost an even greater volume of water. Sodium replacement should therefore always be in the form of hypotonic solutions. This is even more important when treating non-ketotic hyperosmotic coma.

Replacement with 0.45 percent saline solution is recommended. An attempt to hydrate the patient with normal saline solution will not provide the free water that is needed.

Patients recover from ketoacidosis more quickly and become responsive to insulin sooner if alkali is administered early in the treatment program. Blood pH generally ranges from 6.8 to 7.2 and is usually below 7.0 if the patient evidences serious sensorial changes. Therefore, as an initial replacement solution, we recommend half normal saline solution with one vial of sodium bicarbonate (containing 44 mEq) added to each liter. Such a solution has the advantage of providing some free water, of furnishing relatively more sodium than chloride, of providing an alkaline solution and of not containing glucose, which would contribute to an already elevated glucose level and produce a further increase in the osmolality of the extracellular fluid.

The first liter on this solution should be administered within 15 to 20 minutes, and the next two liters should be given over the following 90 minutes. Additional fluid at a rate of 500 ml per hour during the next four hours is usually adequate.

When the patient with diabetic coma is admitted to the hospital, his total body potassium is decidedly depleted, and the serum level reflects dehydration and renal insufficiency with or without acidosis. It is, therefore, expected that soon after the initiation of treatment with insulin and hypotonic saline solution, the serum potassium will fall rapidly to subnormal concentrations. It is difficult to obtain accurate values of serum potassium quickly from the laboratory, and the electrocardiogram correlates poorly with the initial serum potassium level. We therefore routinely begin the administration of potassium soon after effective treatment has been initiated and urine flow estab-

lished. We recommend the administration of potassium one to two hours after the beginning of treatment, to be continued at the rate of 20 to 30 mEq per hour for the next five or six hours. It is further recommended that, when it is available, potassium be given as the phosphate or acetate salt.⁹

Hypotension may occur either as a presenting sign or late in diabetic coma. The hypotension which is part of the presenting manifestations is often due to severe volume depletion and usually responds to intravenous fluid replacement. If the hematocrit at first is low-normal, or is low in spite of a pronounced deficit in fluid volume, these patients often will require blood transfusions. In this circumstance one must consider acute hemorrhagic pancreatitis as the cause of the diabetic ketoacidosis and the blood loss anemia.

The later occurrence of hypotension may reflect diminished peripheral resistance secondary to inappropriate vasodilation and is often responsive to the administration of norepinephrine.¹⁰

When an aggressive approach to the treatment of diabetic coma is undertaken, the patient is usually in a satisfactory state of control within four to six hours, and often wants to eat and drink at this time. We advise prohibiting oral intake for at least 12 hours, because earlier feeding often causes nausea and vomiting.

After the blood sugar is below 250 mg per 100 ml and acetoacetic acid has been eliminated from the plasma, control can be continued by subcutaneous injection of small quantities of crystalline insulin. It is given every four hours and the dose is determined by urine testing. Generally, the patient can be returned to his usual routine of diabetic management the following day.

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Rubella

Technical Problems in the Performance of Hemagglutination-Inhibition (HI) Tests

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■ *The rubella hemagglutination inhibition (HI) test is the most sensitive serologic method available for diagnosis of infection and for determination of immunity status. At present, however, it is not a well-standardized procedure and several modifications are in use. Comparison of results obtained on the same specimens by different laboratories has shown wide variations. The sensitivity and reliability of the technique is decidedly influenced by each of the variables of the test system; these include erythrocytes, antigen, methods employed for removal of non-specific inhibitors and natural agglutinins from test sera, the pH of the diluents and the temperature of incubation. The presence or absence of HI antibody cannot be determined reliably by screening a single low dilution of serum. Commercially available reagents and kits for rubella HI tests vary widely in their reliability. The test should be performed only by experienced persons who understand the principles of the technique and who are aware of the pitfalls and of the importance of using adequate controls in each run.*

THE HEMAGGLUTINATION-INHIBITION (HI) test^{1,2} is the most widely used procedure for determination of rubella (German measles) antibodies. These tests are now commonly employed in clinical practice for the diagnosis of suspected cases of rubella, especially in pregnant women and their immediate contacts and for determining the immune status of pregnant women exposed to rubella.^{3,4} The results of the test and their interpretation may be a determining factor, of consid-

erable concern to the physician and patient, in judgments as to clinical management.

The impending release of live, attenuated rubella virus vaccines⁵ will very likely create a sharply rising demand for rubella HI tests to identify susceptible adolescent and adult women of childbearing age who should be immunized. The risk that the live virus vaccine may result in injury to the fetus if given during pregnancy or shortly before conception, is unknown. Hence administration of the vaccine is absolutely contraindicated during pregnancy and a woman of childbearing age may be given the vaccine only if she understands that it is imperative for her to avoid becoming pregnant

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for the following two months.⁵ The question of whether or not to administer vaccine to a patient of childbearing age is resolved if it can be established by a serologic test that she already possesses antibodies (approximately 75 to 80 percent have antibodies by age 20).

With the development of HI techniques for measuring rubella antibodies and the recent availability of commercial testing kits and reagents, a number of laboratories which have not had previous experience with HI methods are interested in undertaking rubella tests. At present, however, the HI test for rubella is not a standardized technique and several modifications are in use.^{1,2,6,7,8} Comparison of results from different laboratories on the same specimens has shown wide variation. The Medical Laboratory Services Advisory Committee to the Public Health Service has recently warned: "This test is a complex procedure which must be performed by well trained, experienced individuals. In addition, a thorough knowledge of the immune response is essential for the proper interpretation of test results. Because of actions which may be taken on the basis of laboratory results, the need for accuracy is great, and certain problems associated with the HI test must be recognized."

The Viral and Rickettsial Disease Laboratory of the California State Department of Public Health and other virus laboratories are collaborating with the National Communicable Disease Center in Atlanta to assess certain variables in the test and arrive at a standard recommended procedure. The following outline of some of the technical factors and pitfalls in rubella HI test and reagents now in use will assist in understanding the types of difficulties a laboratory is likely to encounter and the wide variation in results on the same specimen which may be obtained by different laboratories.

Technical pitfalls in rubella hemagglutination-inhibition (HI) tests

A. Components of the rubella hemagglutination and hemagglutination-inhibition systems.

1. Hemagglutinating (HA) antigens

a. *Potency of antigen*

Usable rubella HA antigen preparations may vary in titer from 1:32 to 1:1024. Antigens of low titer may contain non-hemagglutinating viral particles which compete with hemagglutinating particles for antibody, and thus give lower anti-

body titers than those which are obtained in tests with high-titered antigens in which non-hemagglutinating particles are diluted out. Since low-titered HA antigens tend to give tests of low sensitivity, "false negative" results may be obtained. Antibody titers of a given serum may vary as much as 8-fold against different antigen preparation.

b. *Effect on antigen titers of other variables in the test system.*

The HA activity of rubella antigens is dependent upon the pH of the diluents, the temperature of incubation and the erythrocytes in the tests. Failure to use optimal pH, temperature and erythrocytes results in less sensitive tests—that is, reduced ability to detect antibody.

c. *Avidity*

Rubella HA antigens prepared by different procedures may vary in their avidity—that is, in their ability to combine with specific antibody. The reasons for these differences in avidity are not known, but may be related to the presence of non-hemagglutinating viral particles in the preparations.

d. *Treatment with chemicals*

To be acceptable and safe for use in diagnostic laboratories, the infectivity of rubella virus HA antigens must be destroyed by treatment with Tween-80 and ether. This may produce changes in the reactivity of the antigen as evidenced by erratic settling of agglutinated erythrocytes and even in spontaneous elution of the hemagglutinins from agglutinated erythrocytes.

2. Diluents used for various reagents

In some of the currently-used rubella HI test procedures the diluents are buffered to give the optimal pH for hemagglutination (pH 6.2) while with other procedures the diluents do not give an optimal pH for rubella hemagglutination. In the latter case the test is less sensitive for detection of antibody. The stability of the antigen may also be influenced by the diluent in which it is suspended. Some of the test procedures employ diluents containing a low concentration of bovine albumin, which facilitates settling of the test erythrocytes and aids in reading the results; others do not. Since the products from each manufacturer are for use in a specific procedure, intermixing reagents from different sources may alter the performance of the test.

3. Erythrocytes used in test

It is essential to use only those species of erythrocytes which are most sensitive to agglutination by rubella virus, viz., pigeon or one-day-old chicken erythrocytes. Failure to do so results in tests of decreased sensitivity. Also, as different lots of cells may vary in their sensitivity to agglutination, a reliable source of erythrocytes of consistent sensitivity is a requisite.

Erythrocytes should be stored no longer than two weeks before use in rubella HI tests. Older erythrocytes hemolyze, tend to agglutinate spontaneously and become less sensitive to rubella hemagglutinins. Some commercially available erythrocytes which have been treated with a preservative to increase their shelf-life have been found to give indistinct patterns of hemagglutination and inhibition, so that accurate reading of results is difficult for the experienced worker, and virtually impossible for the inexperienced.

4. Sera to be tested

a. *Natural agglutinins*

Human sera normally contain natural agglutinins for the test erythrocytes, and these must be absorbed from the sera before valid test results can be obtained. It is important to determine the proper amount of erythrocytes which effectively remove agglutinins and to absorb the sera at 4°C. Human sera appear to contain higher levels of natural agglutinins for pigeon erythrocytes than for chicken erythrocytes and with certain sera it is difficult to absorb out these agglutinins. Residual agglutinins will mask antibody reactions in lower serum dilutions, giving a "false negative."

b. *Nonspecific inhibitors of hemagglutination*

All sera contain fairly high levels of nonspecific inhibitors of rubella virus hemagglutinins. These must be removed from the sera before they are examined for specific antibodies. Failure to remove inhibitors results in "false positive" reactions. Some of the treatments, however, may remove specific antibody as well as non-specific inhibitors.

At this time kaolin treatment is most widely used for removal of rubella HA inhibitors. The koalin must be acid-washed, and it should be recognized that different batches of koalin may vary in their ability to remove inhibitor. The greatest drawback to the use of koalin is that it

may remove specific antibody, particularly IgM antibody. The use of koalin suspended in a buffer at pH 9.0 minimizes absorption of antibody, but not all of the test systems employ koalin at this pH.

The non-specific inhibitors of rubella HA are in the beta-lipoprotein fraction of serum, and this can be specifically precipitated with heparin and $MnCl_2$ without removing specific antibody from the serum. At this time procedures for heparin- $MnCl_2$ treatment are not well standardized. Using too little of the reagents results in incomplete removal of inhibitor, and using too high a concentration of the reagents causes the test serum to agglutinate the test erythrocytes. If sera to be treated with heparin- $MnCl_2$ are diluted in a phosphate buffer, a precipitate is produced which removes specific antibody from the serum.

B. Conditions of incubation of the tests

Rubella hemagglutination occurs optimally at 40°C, although the reaction also takes place at higher temperatures. Some of the test procedures currently in use employ incubation at room temperature; this results in a less sensitive test.

C. Test controls

The dilution of antigen employed in the test must be "back-titrated" to determine that the proper number of antigen units was used. Using too little antigen results in false positive results, while too much antigen gives false negative results. Most test systems employ four units of antigen.

Every test run must include a known negative serum and a positive serum of known titer. The negative control serum should show no inhibition of hemagglutination at a dilution of 1:8 or 1:10, while the titer of the positive serum should vary no more than two-fold from the known median titer. If such results are not obtained in the controls the test is considered invalid.

At least four of the lower dilutions of each test serum should be examined for possible ability to agglutinate the test erythrocytes (incomplete removal of natural agglutinins). If the serum dilutions alone produce agglutination specific rubella antibody, if present, is masked.

Every run must include a number of "erythrocyte controls" consisting of the test dose of erythrocytes and the diluent used for the serum and virus. This indicates whether the erythrocytes settle properly under the test conditions. Erythrocytes

frequently will not settle in improperly cleaned plates or tubes, and this can be mistaken for agglutination.

D. Screening

The presence or absence of rubella antibody cannot be determined reliably by testing only a single, low dilution of serum. Nonspecific agglutination caused by natural agglutinins in serum or improperly cleaned test vessels can lead to incorrect results, which can be recognized only if a range of serum dilutions, dilutions beyond the highest expected serum titer, are tested. Also, determining antibody endpoints can aid in determining the relative sensitivity or insensitivity of each run.

E. Observations on rubella HI test reagents from various commercial sources.

The following observations on commercially available reagents, taken from the experience of this laboratory or reported to us by other laboratories, illustrate the variations or problems which may be encountered. However, manufacturers are continuously striving to improve their products, and difficulties encountered with one lot of a reagent may not apply to other lots from the same manufacturer.

Manufacturer A. Antigens, reference sera and erythrocytes from one-day-old chickens are available. Experience in this laboratory with these reagents has been limited to a single lot of HA antigen referred for testing by a local public health laboratory. The antigen gave a titer of only 1:4, while the indicated titer on the label was 1:32. This antigen was thus not satisfactory for use in rubella HI testing.

Manufacturer B. Kits containing all of the reagents necessary for rubella HI testing are available. The test system does not utilize what is generally regarded as the optimal pH for rubella hemagglutination, and the koalin is not suspended in buffer

at pH 9.0 to minimize antibody absorption. Difficulties have been encountered with low titers of certain lots of antigen, both in this laboratory and in a reference virus laboratory. The patterns of hemagglutination and inhibition produced by the preserved erythrocytes furnished with the kit are difficult to read or interpret.

Manufacturer C. Kits for rubella HI testing are available containing all of the reagents with the exception of erythrocytes, which can be obtained separately. The test system employs the optimal pH for rubella hemagglutination and koalin is suspended in buffer at pH 9.0. In the experience of this laboratory, and also the reference laboratory, the reagents have been found to be satisfactory, and the antigens have been of high titer.

Manufacturer D. Rubella HI testing kits are available. This laboratory has had no experience with the reagents; however, a reference laboratory found the titers of the antigens to be too low for satisfactory performance.

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CASE REPORTS

Benign Micturition Syncope

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THE SUDDEN DEVELOPMENT of unconsciousness in a previously healthy, young or middle-aged patient is always an alarming incident. Unless the reason is immediately apparent a physician must consider and rule out such serious entities as brain tumor, stroke, myocardial infarction and epilepsy. In recent years attention has been drawn to a clinical syndrome in which syncopal attacks associated with urination occur *de novo* in apparently healthy young and middle-aged men. This has been designated "micturition syncope."¹ Although only a dozen cases so diagnosed have been reported, it is felt desirable to bring the attention of physicians to this syndrome. For recognition of the phenomenon and knowing it is invariably benign will permit the omission of costly and time-consuming diagnostic studies and spare the patient much anxiety.

Report of a Case

The patient, a 45-year-old white male schoolteacher, considered himself in excellent health until he had a syncopal attack. The patient said he arose at his usual hour of 6:00 a.m., feeling completely normal. While performing the first micturition of the day in a normal fashion he suddenly became nauseated, felt faint and soon lost consciousness. His wife said she heard him fall to the floor, and then rough, stertorous breathing. She found him propped in a corner of the bathroom completely unconscious, his hands and jaws moving convulsively. After an estimated four or five

minutes he became conscious and recovered normal function. On medical examination approximately two hours later, he said he had no residual effect except weakness and considerable apprehension. There was no history of urgency or pain or difficulty in starting the urinary stream. Specifically questioned, the patient denied straining to initiate the stream and he had no previous history compatible with prostatism, nor of bleeding, polyuria, polyphagia, nausea, vomiting or dark or tarry stools. He had had no chest pain at the time or previously and no respiratory distress. He could not recall coughing at the time of the syncopal episode or for several weeks preceding. He had had no similar episode in the past, had never previously fainted or lost consciousness and had no history of head injury. He neither smoked nor drank and was taking no medication.

On physical examination the patient appeared quite apprehensive and the skin was somewhat ashen. The pulse rate was 60 and blood pressure was 160/90 mm of mercury. No abnormality was noted on neurologic examination. Because of the somewhat unusual circumstances surrounding this episode of fainting the patient was admitted to hospital for observation. Results of physical examination there remained entirely within normal limits and the initial elevation of the blood pressure did not recur. The blood pressure in the hospital averaged 130/80 mm. The stools were always brown and several specimens were negative for occult blood by the usual tests. Several electrocardiograms were normal. An x-ray film of the skull showed no abnormality. The hemoglobin was 14.1 grams per 100 ml of blood and the hematocrit 44 percent. Leukocytes numbered 7,250 per cu mm with a normal cell differential. The fasting blood sugar on the day after admission was 110 mg per 100 ml. Specific gravity of the urine was 1.010 and it was negative for albumin, sugar and acetone. No unusual features were found in the urinary sediment.

As the blood pressure quickly returned to normal in this patient, there appeared no reason to look for pheochromocytoma.

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No further episodes nor any other abnormal symptoms occurred in six years of follow-up of this patient and he remains clinically well.

Comment

Strangely, the first reference to syncope specifically associated with micturition did not occur until 1958. In the report of syncopal episodes of varied causation in 82 presumably healthy young adults, urination is listed as the "clinical incident associated with syncope" in four.² In one of these, however, "fatigue—lack of food—alcoholic ingestion" are also noted, without further comment. In another the patient was in the hospital because myocardial infarction was suspected, and although that suspicion was not substantiated, it at least suggests the added factors of anxiety or functional disease. Nausea was also a symptom in that case.

Since then ten additional cases of what has been called micturition syncope have been described.^{1,3,4}

In only one of the 12 cases was urinary tract disease demonstrated.¹

The following factors were common to the remaining 11 cases, as well as the present one: All the patients were men between 23 and 60 years of age (most between 30 and 46). The episodes occurred at night, almost always soon after arousal from sleep, the act of urination was begun without straining, was painless, free and without symptoms; and the syncopal episode occurred after some urine was passed or after passage was complete. Recurrence is unusual.

The cause of micturition syncope is unknown. Proudfit and Forteza³ have expressed the opinion that Valsalva's maneuver with decreased venous return is responsible. They imply that the maneuver is a normal component of the act of micturition in males. In the normal male without obstruction, straining does not appear necessary to initiate

urination, and the act of cessation of urination is aided by voluntary contraction of the bulbocavernosus and ischiocavernosus muscles. In the seven cases described by Proudfit and Forteza none of the patients is reported as making mention of Valsalva's maneuver.

Etiologically, micturition syncope would appear to be the summation of several physiologic phenomena. It is known that the sudden, rapid shift from the horizontal to the upright position may result in syncope in some persons.⁵ The quiet, erect posture in the male during micturition before he has begun any muscular activity may also contribute to orthostatic hypotension, a situation akin to fainting in soldiers kept at rigid attention. That these postural factors are operative would seem supported by the fact that this syndrome has never been reported in women.

If the Valsalva maneuver were a frequent cause, should not one expect both frequent recurrence and at least some instances during the day?

Summary

A case of micturition syncope is described and the 12 cases previously reported are reviewed.

It appears likely that the cause is not the performance of a Valsalva maneuver, as has been suggested, but rather a summation of failure of orthostatic blood pressure mechanisms.

The condition is benign and unlikely to recur.

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Porphyria Cutanea Tarda

Remission by Venesection

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PORPHYRIA CUTANEA TARDA describes a biochemical abnormality characterized, chemically, by excretion of large amounts of uroporphyrin in the urine and stool. It is a chronic, apparently acquired, disorder and typically appears in 50- or 60-year-old males after many years of excessive intake of alcohol. Ingestion of various drugs and chemicals may also precipitate symptoms.¹ Exposure to more than one hepatotoxin probably accelerates and intensifies the hepatotoxic functional disturbances.²

Clinically the disease is manifested by cutaneous lesions, (which develop on exposure to heat, light and friction), hirsutism and hyperpigmentation. Diabetes mellitus is present in about one out of three patients, and in 80 to 90 percent of cases there is an abnormal liver function test.³ A high proportion of patients have significantly elevated serum iron levels, both free and bound.

No curative treatment has been prescribed, but in 1960 Ippen,⁴ in Germany described pronounced improvement after repeated venesections. More recently, Epstein and Redeker⁵ reported success in reducing symptoms through successive phlebotomies.

Report of a Case

The patient was a 43-year-old white man. Questioning in the course of a routine examination elicited that since a young man he had been subject to numerous blisters on the ears. During the last four to five years he had noticed blisters on the dorsum of both hands, and recently a rash had appeared on the back of his neck. The blistering and rash were aggravated by exposure to the sun, and the lesions persisted. The patient was a heavy con-

sumer of alcoholic beverages and had used them to excess for several years. The only positive physical findings were the extremely fragile blistered hyperpigmented areas covering the posterior neck, dorsum of both hands and the ears.

Hemoglobin, hematocrit, and leukocyte count were within normal limits. Serum iron was in the normal range (96 mcg per 100 ml). Total iron binding capacity (TIBC) was elevated (501 mcg per 100 ml) as was the blood sedimentation rate (40 mm in one hour). There was no indication of facial plethora, polycythemia, siderosis or cirrhosis. Diagnosis of porphyria cutanea tarda was established by the finding of a large amount of porphyrin in the urine (Table 1).

Phlebotomy was performed at approximately two-week intervals, 500 ml of blood being removed each time. A total of 4,600 ml was removed over a period of five months.

Quantitative urine uroporphyrin values were obtained by the Sterling and Redeker method⁶ before treatment began and periodically during therapy. Serum iron, TIBC, hemoglobin and hematocrit values were also determined at intervals.

Table 1 shows the patient's progress during the period of phlebotomy. Uroporphyrin values diminished as expected, except for the unusual increase in December 1965. No explanation was found for the temporary reversal in trend.

Four months after the last phlebotomy, the patient was clinically normal, all signs of rash and blistering having disappeared. Hemoglobin and hematocrit values were normal.

The patient continued his alcohol intake unchanged during and after therapy. He was given a follow-up examination 38 months after the last phlebotomy and he was still clinically asymptomatic.

TABLE 1.—Progress of Phlebotomy Therapy in a Case of Porphyria Cutanea Tarda

	Ml of Blood Removed	Urine Uroporphyrin Mcg per Day	Hemoglobin Gm per 100 ml	Serum Iron Mcg per 100 cc	TIBC Mcg per 100 ml
6/ 7/65	0	8310	13.4
6/14/65	500	96	501
6/28/65	500
7/12/65	500	90	286
7/26/65	600
8/17/65	500	70	430
8/30/65	500
9/20/65	500	4955	12.3
10/ 4/65	500	882	12.1	32	384
11/ 8/65	500	63	305
12/ 6/65	0	1725	13.4	105	510
1/20/66	0	230	13.3	200	390
3/10/66	0	...	13.7	163	390
1/25/69	0	2998	13.9	227	341

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matic with no sign of rash or blisters. However, uroporphyrin in the urine had increased significantly, and the serum iron level had risen above the normal limit.

Comment

In this case, repeated venesection therapy carried out over a relatively short time appeared decidedly to alter porphyrin metabolism. The chemical change was accompanied by a remission in clinical signs to the complete elimination of active clinical disease.

Continued absence of symptoms for so extended a period is encouraging, considering that the patient continued to use alcohol. Spontaneous remissions are known to occur in some patients after prolonged abstinence from alcohol.

There is considerable evidence of an association between iron and abnormal porphyrin metabolism in porphyria cutanea tarda. However, Epstein and Redeker⁵ noted that increased hepatic iron content is not a prerequisite for response to phlebotomy therapy. Other recent studies⁷ indicate that abnormal ferrokinetics with hepatic deposition of iron occur in this disorder, but they do so inconsistently.

Summary

A heavily drinking patient with chemical and clinical evidence of porphyria cutanea tarda was treated by phlebotomy. Removal of 4,600 ml of blood over a five-month period decidedly reduced uroporphyrin excretion with an accompanying remission of the clinical disease, even though the patient did not lessen his intake of alcohol. A follow-up examination after 38 months showed an increase in uroporphyrin excretion but clinical symptoms had not recurred.

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AN INDELIBLE PENCIL FOR ANAL ITCHING

How do you feel about aqueous gentian violet for symptomatic relief of anal pruritis?

"Some years ago a patient came in who had a hot, wet, red bottom; and I wondered whether there was something that I could put on it that would . . . give him a lot of relief. The first thing I saw was an indelible pencil so I painted him with an indelible pencil and told him to use cotton and stop using toilet paper. . . . He came back three days later and said, 'I don't know what you did, but I haven't had any itching since.' So on all of my treatment tables, there's an indelible pencil.

"Now what is an indelible pencil? It's gentian violet, but gentian violet in a higher percentage than you can get in solution (a saturated solution of gentian violet is 2 percent whereas an indelible pencil is about 90 percent. I think it has a binder added). Using dyes like gentian violet is well and good except . . . that you've got to recognize that most of them are alkaline in nature, and you can't use them more than twice a week. If you do, you're going to actually worsen the condition."

—MATTHEW A. LARKIN, M.D., Miami

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Congenital Adrenal Cortical Hyperplasia—Successful Long-Term Treatment

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IT IS ALMOST TWO DECADES since Wilkins and co-workers¹ first reported the success of cortisone treatment of the congenital adrenogenital syndrome with adrenal hyperplasia. Since that time the pathophysiology of this syndrome has been delineated and several variants have been described. The subject was thoroughly reviewed recently by Bongiovanni and Root.² The number of cases of successful long-term therapy in male children, however, has not been extensive. Experience with such a case, in which the patient was treated with corticosteroids from early childhood for over 15 years, prompts this report.

Report of a Case

The patient was born in January 1952, an apparently normal male, weighing 9 pounds 6½ ounces. Soon after birth intractable vomiting developed and he became dehydrated. He was therefore admitted to Letterman General Hospital at 8 weeks of age with a weight of 7 pounds 5 ounces. Parenteral therapy restored fluid and electrolyte balance, and because of the possibility of congenital hypertrophic pyloric stenosis, celiotomy was performed. No gastrointestinal abnormalities were found; nevertheless a Ramstedt procedure was performed. The patient withstood the surgical operation well. However, when oral feedings were resumed vomiting recurred. At this point, hyponatremia and hyperkalemia were demonstrated and a



Figure 1.—Secondary sexual development at age 3 years 7 months. Despite the enlarged phallus and pubic hair development, testicular size was normal for the age.

therapeutic trial of desoxycorticosterone acetate (DOCA) with supplemental sodium chloride was begun. In two days vomiting ceased and body weight stabilized. After two weeks of therapy, DOCA was discontinued. Within 48 hours vomiting recurred. DOCA was given again and the child did well for the remainder of the stay in hospital. Two 24-hour urinary 17-ketosteroid determinations were performed, and both were above normal range at 1.7 and 1.5 mg (normal at this age, 0.1 to 1.0 mg). The patient was discharged 26 May 1952 on a high sodium supplementation and 5 mg of DOCA intramuscularly daily. Six months later the child could be maintained on sodium supplementation without DOCA.

When the patient was 18 months old, the mother first noted rapid growth. Because of the belief it was secondary to the DOCA he had received, it was not until two years later that she brought him to the Letterman Pediatric Clinic for evaluation of precocious growth and development. At that time, the child was 3 years 7 months of age, and he had the appearance of a 6- to 7-year-old child. He had a bone age of 7 to 9 years, a height age of 5½ years (45½ inches tall), pubic hair

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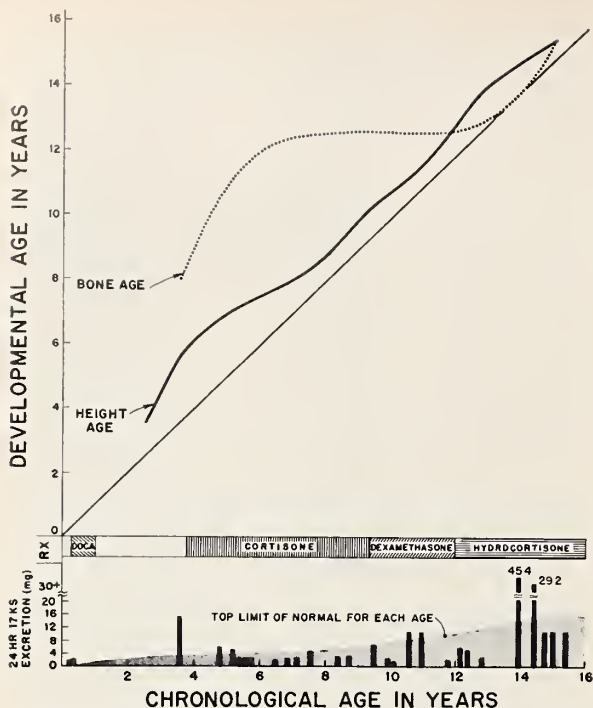


Chart 1.—Effects of treatment on height, bone maturation, and urinary 17-ketosteroid excretion. The relatively low 17-ketosteroid excretion around age 12 occurred when the patient was clinically Cushingoid.

development, and a phallus 6.5 cm in length (Figure 1).

His blood pressure was 80/40 mm of mercury. Urinary 17-ketosteroid excretion was again elevated at 15 mg in 24 hours (normal at this age, 1 to 4 mg). An intravenous pyelogram showed no abnormality, and serum sodium and potassium levels were within normal limits. Chromosome analysis revealed a male genotype. At this time, the patient was first seen by one of the authors. A diagnosis of a congenital adrenogenital syndrome was made and continuous therapy was begun, at first with intramuscular cortisone, later with oral dexamethasone, and then with hydrocortisone. Doses varied over the years from 40 to 75 mg hydrocortisone equivalent daily, the amount depending on urinary 17-ketosteroid excretion patterns and clinical course. The average dose necessary to maintain normal 17-ketosteroid excretion was 60 mg of hydrocortisone per day.

When the patient completed normal puberty and reached a maximal height of 57½ inches and a bone age of 17 years during his sixteenth year, steroid therapy was gradually tapered to discontinuance. Although he remained asymptomatic during this period, endogenous cortisol production

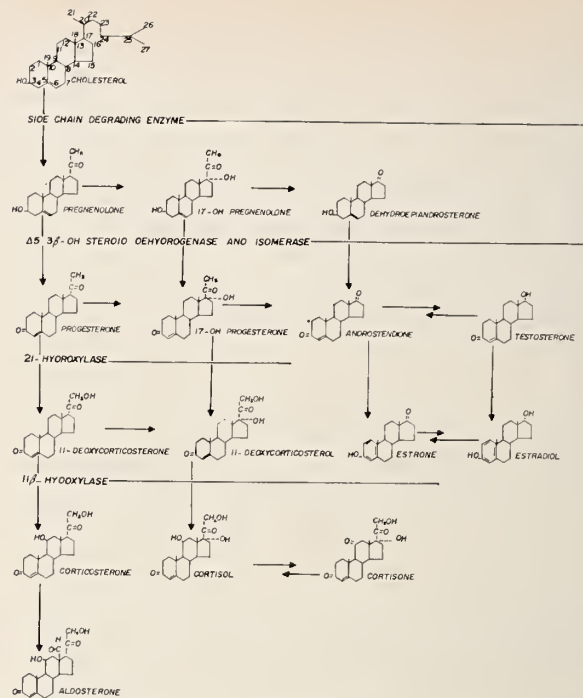


Chart 2.—Sequence of steroid genesis. In the condition reported, a relatively impaired 21-hydroxylation leads to decreased production of mineralocorticoids (including DOCA) and glucocorticoids (including cortisol).

did not resume over a nine-month period and replacement therapy with 10 mg of hydrocortisone twice daily was reinstituted. (See Chart 1.)

At no time during the period of corticosteroid therapy had the patient shown evidence of adrenal insufficiency. He had varicella, measles, and a leg fracture without requiring any additional steroids. Except for a period at age 12 when he was receiving 75 mg of hydrocortisone daily and had "over-suppression" of his urinary 17-ketosteroids, clinical signs of Cushing's syndrome were never apparent.

Discussion

Clinically, the history in this case is quite typical of a congenital 21-hydroxylase deficiency. In this condition, a relatively impaired 21-hydroxylation leads to decreased production of mineralocorticoids (including DOCA) and glucocorticoids (including cortisol). (See Chart 2). The patient's mineralocorticoid production was so small that he required exogenous DOCA during his early life, while his decreased cortisol production was manifested later.

Diminished cortisol formation results in increased ACTH stimulation, causing the accumula-

tion of excessive amounts of steroids before the C-21 block. These substances include dehydroepiandrosterone, androstendione and androsterone, which all have potent androgenic potentials. Exogenous corticosteroid therapy serves to inhibit this excessive ACTH secretion and consequently reduces the excessive production of these hormones.

Most of the reported cases of the adrenogenital syndrome have been in females; in one series³ 78 percent were female. This high proportion, probably does not reflect the true incidence, but the condition is more frequently suspected in females due to their anomalous genitalia at birth. As in the present case, the male's genitalia are normal for the first several months of life. For this reason, male infants with an unrecognized defect may die in infancy from dehydration and circulatory collapse, or from hyperkalemia and cardiac arrest. Frequently, as in the present case, the intractable vomiting leads to a misdiagnosis of hypertrophic pyloric stenosis. Iverson⁴ reported a fatal outcome in all of 81 patients who received no specific therapy. Such statistics emphasize the need for awareness of this condition in the male infant with symptoms resembling an Addisonian crisis developing a few weeks after birth. The finding of elevated urinary 17-ketosteroids should confirm the diagnosis.

In the absence of such an early complication, the disease usually goes unrecognized until inordinate growth and maturation become apparent around 2 years of age. At this time, one must consider constitutional precocity and virilizing adrenal tumor in the differential diagnosis. Small testicular size is of help in eliminating the former, and adequate suppression of the elevated 17-ketosteroids upon the administration of cortisol eliminates the latter.

Although the androgen excess is not so critical a problem in the male child as it is in the female in regard to sexual maturation, the effect on acceleration of bone age makes early therapy essential.

The administration of appropriate doses of glucocorticoid hormones may produce gratifying results in prompt deceleration of growth so that ultimate normality can be achieved in height, sexual maturation and fertility. To achieve these good results, the child must be closely monitored with urinary steroid determinations, bone age radiographs, and serum electrolyte studies.

Therapy must be continued indefinitely in children who manifest the salt-losing variety, and in all females. There have been dissenting opinions, however, in regard to whether life-long treatment is necessary in uncomplicated cases in males.^{2,5}

It seems most reasonable to us that the relative Addisonian state which most of these patients have is enough reason in itself to advise life-long therapy. The development of an adrenal neoplasm occurring in a patient who has had continuous ACTH excess as the result of the adrenogenital syndrome has been seen in at least one instance.⁶ Such a report adds increased impetus to the recommendation for continuous therapy in all cases.

Summary

A case is described of a 16-year-old male with the adrenogenital syndrome with adrenal hyperplasia, due presumably to a 21-hydroxylase deficiency, who has been successfully treated for over 15 years with corticosteroids. The problem of early diagnosis in male infants and the gratifying results of long-term suppressive therapy are emphasized.

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Chemotherapy Guide

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THIS REVIEW IS intended as a guide to proper antimicrobial therapy rather than as an exhaustive, definitive compendium. The outline format was selected to make the material more useful as a ready reference source and to permit early publication, insuring up-to-date data. Much of the presentation requires weighing of one agent against another; every effort has been made to avoid arbitrary or biased interpretations.

The material is organized into sections as follows: sulfonamides (sub-organized into various classes), antibiotics and other antibacterials (arranged in groups, where possible), drugs of choice for specific bacteria, investigational antimicrobial agents (the more promising agents), the use of antibacterial agents in renal insufficiency, and antibiotics and liver disease. Other material which might have been useful (information on antimycobacterial and antiparasitic drugs, principles of antibacterial chemotherapy, additional pharmacologic information, therapy of infectious diseases requiring special regimens, etc.) has been left out in the interest of brevity.

Doses given are for adults. In the presence of impaired renal function, it may be important that

dosages be reduced since most antibiotics are principally excreted in the urine. For specific information on this see section "Antibacterial Agents in Renal Insufficiency" by Dr. Ziment.

Superinfections are not mentioned as side effects but may be encountered with any of these agents. They are more likely to occur after the use of "broad-spectrum" agents, which suppress more of the normal flora.

SULFONAMIDES

SYDNEY M. FINEGOLD, M.D., AND ALVIN DAVIS, M.D.

The therapeutic effectiveness of sulfonamides is reduced by pus, necrotic tissue, heavy inocula of organisms and thick fibrin barriers at the periphery of a lesion. Hence, sulfonamide therapy is optimally effective in mild and moderate infections which exhibit minimal suppuration.

I. PRESENT-DAY USES:

A. Urinary infections — chiefly those due to *E. coli*.

B. Meningococcal infections — only if organism known to be sensitive. No longer drugs of choice.

C. *Nocardia* infections—treatment of choice.

D. Bowel surgery — pre- and post-operatively; sulfasuxidine, sulfathalidine.

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E. Trachoma, inclusion conjunctivitis — in conjunction with tetracycline.

F. Dermatitis herpetiformis.

G. Rheumatic fever prophylaxis.

H. South American blastomycosis — not as good as amphotericin.

I. Protozoan infections (malaria, toxoplasmosis, *Pneumocystis* infections) — together with pyrimethamine.

J. Glanders, melioidosis.

K. Lymphogranuloma venereum, chancroid.

L. Gastrointestinal tract inflammations — regional enteritis, ulcerative colitis. Intestinal sulfonamides (D above) and Azulfidine.

M. Prevention and treatment of *Pseudomonas* infection of burns (mafenide).

N. Other topical uses—ophthalmic and vaginal.

II. SHORT-ACTING SULFONAMIDES:

A. Sulfadiazine:

1. Oral dosage

a. 1.0 Gm q 4 h for systemic infections after 3-4 Gm loading dose.

b. 0.5 - 1.0 Gm q 6 h for urinary tract infections.

2. Intravenous or subcutaneous use (sodium sulfadiazine) — initial dose of 3-5 Gm in a concentration of 0.5-5.0% in N/S, then 2-3 Gm q 6-12 h.

B. *Triple Sulfa*: Higher solubility than sulfadiazine *in vitro*, but crystalluria may occur. Oral dosage as for sulfadiazine.

C. *Sulfisoxazole (Gantrisin)*: Only advantage over sulfadiazine is higher solubility.

1. Dosage—oral—1.0-2.0 Gm q 4-6 h for systemic infections after 3-4 Gm loading dose.

2. Intravenous or intramuscular — Same as oral dosage.

D. *Sulfisomidine (sulfasomidine, sulfadimetine, Elkosin)**: low acetylation in urine. Useful for urinary infections primarily.

E. *Sulfamethylthiadiazole (sulfamethizole, Thio-sulfil)**: low acetylation, rapid excretion. Useful only for urinary infections.

F. *Sulfachlorpyridazine (Sonilyn)**—Very soluble. Particularly useful for urinary tract infections.

G. *Sulfamethazine (sulphadimidine)* — Used mainly in triple sulfa in U.S.

III. INTERMEDIATE-ACTING SULFONAMIDES: Only advantages are convenience and low cost. Slow excretion may be a disadvantage in the event of a reaction.

A. *Sulfaethidol (Sul-Spansion and Sul-Spantab)*: liquid or tablets in sustained release form. Dosage —1-3 Gm (10 ml or 2 tabs) q 12 h.

B. *Sulfamethoxazole (Gantanol)*: Resembles sulfisoxazole but is absorbed and excreted more slowly; more likely to cause crystalluria. Dosage 2.0 Gm stat, then 1.0 Gm q 12 h.

C. *Sulfaphenazole (Sulfabid)*—Similar to sulfamethoxazole.

D. *Lipid Suspensions of Sulfonamides*: available for sulfadiazine, triple sulfa, and sulfisoxazole.

IV. LONG-ACTING SULFONAMIDES: These preparations should not be used because of their toxicity.

A. *Sulfamethoxypyridazine (Kynex, Midicel)*

*Dosage is the same as for sulfadiazine.

B. *Sulfamethoxydiazine* (*Sulfameter*, *Sulla*)

C. *Sulfadimethoxine* (*Madribon*)

D. *Sulphormethoxine*—Very long-acting; therapeutic blood levels for 1 week.

V. POORLY ABSORBED SULFONAMIDES:

for local use in the intestinal tract only.

A. *Succinylsulfathiazole* (*Sulfasuxidine*):

1. Dosage—3.0 Gm q 4 h p.o.

2. Maximum effect usually not achieved until 7th day of therapy.

B. *Phthalylsulfathiazole* (*Sulfathalidine*):

1. Dosage—1.5 Gm q 4 h p.o.

2. Double this dosage in the presence of diarrhea.

3. Effect produced in 5-7 days.

C. *Para-nitrosulfathiazole* (*Nisulfazole*): Used only for intrarectal instillation in treatment of proctitis or non-specific colitis.

VI. TOPICAL SULFONAMIDES:

A. *Mafenide* (*Sulfamylon*): Used on skin as 10% cream. Unlike other sulfonamides, effective in presence of pus and necrotic tissue and does not sensitize readily when used topically. Of value in prevention and therapy of burn infection due to *Pseudomonas*.

B. *Ophthalmic preparations*: Sodium sulfacetamide (*Sulamyd*) and sulfisoxazole diolamine are the only products suitable for topical use in the eye; they are available as solutions (30%) and ointments (10%).

C. *Vaginal preparations*: These include sulfisoxazole and triple sulfonamide combinations made up as creams or tablets. They are used in nonspecific vaginitis and cervicitis.

VII. SULFAPYRIDINES:

A. *Sulfapyridine*: Too toxic for general use, but best drug available for dermatitis herpetiformis.

B. *Salicylazosulfapyridine* (*Azulfidine*): Of value in ulcerative colitis, particularly in preventing relapse. Value in regional enteritis less well established.

VIII. SULFONAMIDES IN GENERAL:

A. Desired peak blood level—8-15 mg/100 ml (except poorly absorbed compounds).

B. Mode of action—bacteriostatic.

IX. TOXICITY AND SIDE EFFECTS:

A. Fever

B. Rash, urticaria

C. Cyanosis, methemoglobinemia

D. Nausea, vomiting, diarrhea

E. Hepatitis, jaundice

F. Hematuria, albuminuria, crystalluria, toxic nephritis.

G. Headache, mental depression, psychosis, peripheral neuritis.

H. Leukopenia, agranulocytosis, purpura, aplastic anemia, hypoprothrombinemia, hemolytic anemia.

I. Severe hypersensitivity reactions — anaphylaxis, periarteritis nodosa and other collagen diseases, Stevens-Johnson syndrome.

X. PRECAUTIONS:

A. Keep careful record of urine output — try to maintain output of at least 1200-1500 ml/24 hrs.

B. Alkalinization of urine—sodium bicarbonate (12-15 Gm/day) may be used for this purpose when full systemic doses of sulfonamides are used, when there is difficulty in being sure of adequate fluid intake and output, and when such adjunctive therapy is not contraindicated.

C. Check fresh urine specimens for RBC's, albumin and sulfa crystals.

D. Weekly blood counts.

ANTIBIOTICS AND ANTIBACTERIALS, GENERAL

SYDNEY M. FINEGOLD, M.D., AND ALVIN DAVIS, M.D.

I. PENICILLIN G (Benzylpenicillin):

1. *Spectrum and Uses*: Highly active against Gram-positive cocci other than beta lactamase-producing staphylococci; Gram-negative cocci; Gram-positive bacilli; fusiforms and some other Gram-negative anaerobic bacilli; and (in high dosage) *Proteus mirabilis*. Oral penicillin G is useful in many urinary tract infections due to *E. coli* and *P. mirabilis*.

2. *Types of Preparations, Route of Administration and Dosage*:

a. *Crystalline aqueous penicillin G*:

(1) Peak blood levels — generally 1-2 units/ml for each one million units intramuscular/day.

(2) Probenecid (Benemid) 0.5 Gm q 6 h will usually raise levels 1½ to 2 times.

b. *Procaine penicillin G suspended in oil or water:*

(1) With single intramuscular dose of 300,000 to 600,000 units, peak serum levels are usually 0.75 unit/ml or less and serum concentrations of at least 0.04 unit/ml (adequate for highly sensitive organisms such as pneumococci and Group A beta-hemolytic streptococci) persist for from 20 to 24 hours. Frequency of administration depends on preparation and dosage used.

(2) Increasing dosage primarily prolongs duration of blood level rather than raising peak level; the usual daily maximum should be 1.2 million units.

c. *Procaine penicillin G in sesame oil and 2% aluminum monostearate:*

A single 200,000 unit dose behaves much like procaine penicillin, but 600,000 unit doses result in levels of 0.03 units/ml or higher for more than 90 hours.

d. *Benzathine penicillin G (dibenzylethylene-diamine dipenicillin G, DBED, Bicillin):*

(1) Very insoluble salt. 300,000 unit dose intramuscularly gives levels above 0.03 unit/ml for over 5 days with peak levels above 0.15 unit/ml uncommon at any time. Doses of 600,000 units and 1,200,000 units intramuscularly result in prolongation of levels to 12 and 28 days, respectively. (The oral form is poorly absorbed and should not be used.)

(2) Chiefly useful as a prophylactic agent and in the treatment of early syphilis.

(3) Painful on injection. Allergic reactions, when they occur, may be severe and prolonged.

e. *Oral penicillin G:*

For urinary tract infections, 400,000 units q 6 h.

3. *Toxicity, Side Effects, and Precautions:*

a. Central nervous system toxicity may occur when unusually high doses are used and/or impaired renal function exists.

b. The amount of potassium injected must be considered when very large doses of crystalline aqueous potassium penicillin are used in the presence of impaired renal function. Each 15

million units supplies 975 mg (25 mEq) of potassium.

c. Allergic reactions ranging from minor skin reactions to anaphylactic shock and death occur. The best prophylaxis is a careful history combined with discriminate use of this drug. The usual skin tests and conjunctival tests with penicillin G are unreliable. Use of penicillinase (Neutrapen) for treatment of penicillin allergy should be condemned because there is no proof of its effectiveness and because it may actually increase the hazard.

d. Hemolytic anemia, neutropenia.

4. *Mode of Action:* Bactericidal.

II. ALPHA-PHENOXY-PENICILLINS:*

A. *Phenoxymethyl penicillin (penicillin V, Pen-Vee, V-Cillin):* This compound is better absorbed on oral administration than penicillin G and is more acid stable. The antibiotic spectrum of the two agents is similar. Both are susceptible to staphylococcal beta lactamase. Most infections which will respond to oral therapy can be treated with 250-500 mg q 8 h. Infections such as osteomyelitis or subacute bacterial endocarditis (when they can be treated orally) require >50-1,000 mg q 4-6 h. Penicillin V is not ordinarily useful for therapy of urinary tract infections.

B. *Phenoxyethyl penicillin (phenethicillin, Syncillin, Maxipen, Chemipen, Broxil, Dargil, Alpen):* This compound is very similar to penicillin V.

III. BETA LACTAMASE-RESISTANT PENICILLINS:*

A. *Methicillin (Staphcillin, Celbenin, Dimocillin):*

1. *Spectrum and Uses:* Active vs staphylococci resistant to penicillin G (beta lactamase-producers). Distinctly inferior to penicillin G vs. other organisms.

2. *Routes of Administration and Dosage*

a. Intramuscularly 1 Gm q 3-6 h.

b. Intravenously 1-4 Gm q 4-12 h (12 Gm or more/day in severe infections). It is best given in 50-100 ml over a 30 minute period q 4-6 h. (The drug is relatively unstable, particularly at acid pH's. Make up just before use.)

*These agents exhibit cross-allergenicity with penicillin G. Probenecid blocks excretion of all penicillins. All are bactericidal.

3. *Toxicity, Side Effects and Precautions*

a. Sensitivity reactions, as with penicillin G.

b. Renal damage (hypersensitivity?) — fever, albuminuria, pyuria, hematuria, oliguria to anuria, nitrogen retention, edema, and eosinophilia may occur. This is apparently reversible, but complete recovery may take months.

c. Bone marrow depression (neutropenia) occurs occasionally.

d. Hemolytic anemia.

e. Each 4 Gm of drug supplies 230 mg (10 mEq) of sodium (drug supplied as sodium salt).

4. *Miscellaneous*. Moderately resistant staphylococci have been isolated rarely. When other agents are to be administered simultaneously, they should be given separately rather than being mixed with the methicillin.

B. *Oxacillin (Prostaphlin, Resistopen)*:

1. *Spectrum and Uses*: Similar to methicillin, but somewhat more active on a weight basis. There is greater protein binding with this agent.

2. *Routes of Administration and Dosage*:

a. Oral—not recommended (cloxacillin or dicloxacillin are preferred oral agents).

b. Intramuscularly—0.5-1.0 Gm q 4 h.

c. Intravenously—0.5 Gm or more q 4 h. May be administered by method described for methicillin.

3. *Toxicity, Side Effects and Precautions*:

a. Sensitivity reactions as with penicillin G.

b. Neutropenia (rare).

c. Reversible SGOT elevations are occasionally noted.

4. *Miscellaneous* — cross-resistance with methicillin. Greater amount of biliary excretion than with methicillin. Not suitable for treatment of meningitis.

C. *Cloxacillin (Tegopen)*:

1. *Spectrum and Uses*: Same as for oxacillin.

2. *Routes of Administration and Dosage*: Available only for oral use. Dosage is 0.5-1.0 Gm q 6 h.

3. *Toxicity, Side Effects and Precautions*:

a. Same as for oxacillin.

b. Nausea, epigastric distress, diarrhea, bitter taste.

4. *Miscellaneous*: Preferred over oral oxacillin because of better absorption and thus higher and more prolonged blood levels. Not suitable for treatment of meningitis.

D. *Dicloxacillin (Dynapen, Veracillin)*:

1. *Spectrum and Uses*: Same as for oxacillin.

2. *Routes of Administration and Dosage*: Available only for oral use. Dosage is 0.25-1.0 Gm q 6 h.

3. *Toxicity, Side Effects and Precautions*: Same as for cloxacillin.

4. *Miscellaneous*: Peak serum levels approximately twice those with cloxacillin at comparable dosage.

E. *Nafcillin (Unipen)*:

1. *Spectrum and Uses*: Similar to oxacillin.

2. *Routes of Administration and Dosage*:

a. Oral—absorption not reliable.

b. Intramuscularly—0.5 Gm q 4-6 h.

c. Intravenously—0.5-1.0 Gm q 4 h. May be administered by method described for methicillin.

3. *Toxicity, Side Effects and Precautions*: As with oxacillin.

4. *Miscellaneous* — Significant biliary excretion.

IV. BROAD-SPECTRUM PENICILLINS:*

A. *Ampicillin (Penbritin, Polycillin)*:

1. *Spectrum and Uses*:

a. Active vs most strains of *Proteus mirabilis* and occasional strains of other *Proteus* species. Active vs most strains of *H. influenzae*, *Salmonella* and *Shigella*, and about 50% of *E. coli* strains.

b. Similar to penicillin G in its activity vs Gram-positive cocci and vs anaerobes except that it is more effective vs many strains of enterococcus.

c. Susceptible to action of beta lactamase and therefore not effective vs most strains of *S. aureus*.

2. *Routes of Administration and Dosage*:

a. Oral—0.5-1.0 Gm q 4-6 h (probably best given one-half hour to an hour before meals).

b. Intramuscularly—0.5-1.0 Gm q 4-6 h.

c. Intravenously — 1.0-2.0 Gm or more

*These agents exhibit cross-allergenicity with penicillin G. Probenecid blocks excretion of all penicillins. All are bactericidal.

q 4 h; may be administered in the same way as recommended for methicillin.

3. *Toxicity, Side Effects and Precautions:*

- a. Sensitivity reactions as with penicillin G.
- b. Bone marrow depression.
- c. SGOT elevation (occasional).
- d. Diarrhea (may be fulminant).
- e. Moniliasis and other superinfections are more frequent than with other (narrower spectrum) penicillins.

4. *Miscellaneous* — Significant biliary excretion.

V. CEPHALOSPORINS:

A. *Cephalothin (Keflin):*

1. *Spectrum and Uses:*

a. Active vs most strains of *P. mirabilis* and some strains of other *Proteus* species and vs most strains of *Salmonella* and *Shigella*. Active vs approximately 50% of strains of *Klebsiella-Enterobacter* and *E. coli*. It is not particularly active vs *H. influenzae*.

b. Similar to penicillin G in its activity vs Gram-positive cocci other than *S. aureus* but less active vs pneumococci. It is less active vs most anaerobes.

c. Resistant to beta lactamase and therefore effective vs penicillin-resistant *S. aureus*.

2. *Routes of Administration and Dosage:*

Not acid-stable; must be given parenterally.

a. Intramuscularly—0.5 Gm q 6 h for average case. Up to 1.0 Gm q 4 h in severe or relatively resistant infections.

b. Intravenously—0.5 Gm q 6 h to 2.0 Gm q 3 h or more. May be administered by method described for methicillin.

3. *Toxicity, Side Effects and Precautions:*

a. Probably cross-allergenic with penicillins. Same type of side effects as with penicillins.

b. SGOT elevation (occasional).

c. Superinfections, particularly with *Pseudomonas*.

4. *Mode of Action*—bactericidal.

B. *Cephaloridine (Loridine):*

1. *Spectrum and Uses:*

a. Essentially the same as for cephalothin, except that it is more active against susceptible anaerobic organisms than is cephalothin.

2. *Routes of Administration and Dosage:* available only for parenteral use.

a. Intramuscularly — 0.5-1.0 Gm q 6 h. Approved use of drug at the time of this writing restricts maximum daily dose to 4 Gm/day.

b. Intravenously—0.5-1 Gm q 6 h. May be administered by method described for methicillin. Maximum approved dose by this route is 4 Gm/day as well.

3. *Toxicity, Side Effects and Precautions:*

a. Nephrotoxicity has occurred when drug is administered in doses in excess of 4 Gm/day. This has usually occurred in patients with impaired renal function. However, all patients treated with this drug should be observed carefully and frequent urinalysis and serum creatinine levels should be obtained. This drug should not be used in patients with impaired renal function.

b. Cross allergenicity with cephalothin and possibly with penicillins as well.

c. Hematologic abnormalities — transient leukopenia, eosinophilia, hemolytic anemia (rare).

d. Superinfections, particularly *Pseudomonas*.

4. *Mode of Action*—bactericidal.

VI. STREPTOMYCIN:

1. *Spectrum and Uses:* Should never be used alone because of extremely rapid development of resistance by various bacteria. In combination with other agents, this drug is useful in tuberculosis, enterococcal infections, in endocarditis due to various organisms, in granuloma inguinale, and in *Pasteurella* infections.

2. *Routes of Administration and Dosage:* Intramuscularly—0.5-1.0 Gm q 12 h to 1.0 Gm 2-3 times weekly.

3. *Peak Blood Levels:* 20-40 mcg/ml after dose of 0.5-1.0 Gm.

4. *Toxicity, Side Effects and Precautions:*

a. Dermatitis (may be severe), drug fever.

b. Nephrotoxicity.

c. VIII nerve damage — primarily vestibular.

d. Bone marrow depression (uncommon).

e. Intraperitoneal, intrapleural, or rapid intravenous administration, particularly in association with ether anesthesia, may result in curare-like effect with respiratory paralysis. Neostigmine is the antidote of choice.

5. *Mode of Action:* Bactericidal.

VII. TETRACYCLINES:

1. *Spectrum and Uses*: Active against many Gram-positive and Gram-negative bacteria, vs rickettsiae, *Mycoplasma* and *Chlamydia* (Bedsonia). Most *S. aureus* are resistant. Twenty percent of Group A beta-streptococci are resistant, and occasional pneumococci are resistant.

2. *Routes of Administration and Dosage*:

a. Oral—

(1) Tetracycline, oxytetracycline, and chlortetracycline—250-500 mg q 6 h.

(2) Demethylchlortetracycline and methacycline—150 mg q 6 h or 300 mg q 12 h.

(3) Doxycycline—100 mg q 12 h x 3 doses, then 100 mg daily.

b. Intramuscularly—

(1) Tetracycline and oxytetracycline — 100 mg q 8-12 h.

(2) Rolitetracycline—350-700 mg daily in 1 or 2 injections.

c. Intravenously—

(1) Tetracycline, oxytetracycline, and chlortetracycline—500 mg q 8-12 h (by slow drip only).

(2) Rolitetracycline—350-700 mg q 12 h (over 15-30 minute period).

3. *Peak Blood Levels*:

a. Oral or Intramuscular—0.5-3.0 mcg/ml.

b. Intravenous—8-10 mcg/ml.

4. *Toxicity, Side Effects, and Precautions*:

a. Oral.

(1) Nausea, vomiting, anorexia, epigastric distress.

(2) Diarrhea, flatulence, proctitis.

(3) Stomatitis, glossitis.

(4) Dermatitis.

(5) Accumulation in teeth and bones — may cause pigmentation and enamel defects in teeth of children.

(6) Anaphylactoid reactions (rare).

(7) Phototoxic reactions (more common with DMCT).

(8) Vaginitis.

b. Intramuscular—local pain.

c. Intravenous.

(1) Thrombophlebitis

(2) Hepatotoxicity may be seen with daily doses exceeding 1.5 grams. With intravenous usage this may be accentuated (or found at

lower dose levels) in the presence of impaired kidney function and/or pregnancy.

d. DMCT—May show, in addition to items listed above in 4. a, nephrogenic diabetes insipidus.

e. Special toxicity in the presence of impaired renal function (may be delayed).

(1) Increasing azotemia, acidosis, hyperphosphatemia.

(2) Anorexia, nausea, emesis.

(3) Weight loss.

(4) Increased urinary losses of nitrogen and sodium.

These effects may be avoided by reduced dosage. They are reversible. Anabolic steroids may prevent or retard these effects also.

f. Special toxicity with outdated drug—Fanconi syndrome may occur (reversible).

5. *Mode of Action*: Bacteriostatic.

6. *Miscellaneous*: The antibacterial activity of tetracycline is counteracted by certain multivalent metallic ions. Therefore, it is best to avoid concurrent administration of such things as aluminum hydroxide gel, milk, etc.

7. *Types of Tetracycline Preparations Available*:

a. Tetracycline (Achromycin, Cosa-tetracylin, Panmycin, Polycycline, Steclin, Sumycin, Tetracylin, Tetrex).

b. Oxytetracycline (Terramycin).

c. Chlortetracycline (Aureomycin).

d. Demethylchlortetracycline (Declomycin, DMCT).

e. Methacycline (Rondomycin).

f. Doxycycline (Vibramycin).

g. Rolitetracycline (Syntetrin, Velacycline).

These drugs are very similar chemically and biologically. There may be some quantitative differences in antibacterial activity against certain species or strains; oxytetracycline seems to be generally superior to the others against *Pseudomonas*. There is virtually complete cross-resistance between the various agents.

VIII. CHLORAMPHENICOL (Chloromycetin)

1. *Spectrum and Uses*: Active against many Gram-positive and Gram-negative bacteria, rickettsiae and *Chlamydia* (Bedsonia). Best drug for typhoid fever. In a number of localities, significant numbers of staphylococci are resistant.

2. Routes of Administration and Dosages:

a. Oral—0.5 Gm q 6 h. Occasionally higher dosages are indicated.

b. Intramuscular—Must not be used by this route; absorption not dependable.

c. Intravenous — Chloramphenicol succinate 0.5 Gm q 4-6 h, each dose administered in 50 ml over 15 minute period.

3. Peak Blood Levels: 10-20 mcg/ml, by any of above routes.

4. Toxicity, Side Effects and Precautions:

a. Bone marrow depression (any or all elements); may be fatal. In rare instances, there is idiosyncratic bone marrow depression unrelated to dosage; apparently more common in white female children and after multiple courses. In most patients, however, toxicity is well correlated with dosage and blood levels and with duration of treatment. Elevation of serum iron and drop in reticulocyte count are early signs of toxicity. Complete blood counts should always be done at regular intervals.

b. "Gray syndrome" in premature and neonatal infants.

c. Optic or peripheral neuritis (rare).

5. Mode of Action: Primarily bacteriostatic.

6. Miscellaneous: There may be a greater hazard of toxicity in patients with impaired liver function. Biliary excretion is poor.

IX. MACROLIDES:

A. *Erythromycin* (*Erythrocin*, *Ilosone*, *Ilotycin*):

1. *Spectrum and Uses*: Active against Gram-positive organisms primarily. Fifteen percent or more of *S. aureus* strains are resistant in some areas. Usefulness in staphylococcal infections (as a single agent) limited by initial resistance or development of resistance. Also useful in *Hemophilus* and *Mycoplasma* infections.

2. Routes of Administration and Dosage:

a. Oral or Intravenous—0.5 Gm q 6 h.

b. Intramuscular — 100 mg q 8-12 h. Give deep intramuscularly.

3. Peak Blood Levels:

a. Erythromycin base or stearate (*Ilotycin*, *Erythrocin*) 0.5-3.0 mcg/ml.

b. Erythromycin estolate (propionyl erythromycin lauryl sulfate, *Ilosone*)—Levels 2-3 times those with erythromycin base or stearate and more consistent. This compound is available only for oral administration.

4. Toxicity, Side Effects, and Precautions:

a. Diarrhea, occasional nausea and vomiting.

b. Mild rash (infrequent).

c. Anaphylaxis (rare).

d. Intrahepatic cholestasis with jaundice is seen occasionally in patients on erythromycin estolate. Eosinophilia (in the peripheral blood) occurs with this. The syndrome is a hypersensitivity phenomenon, occurring typically when the drug is taken for 10 days or more or in repeated courses. The symptoms may recur, in sensitive patients given another course, within 48 hours or even after a single dose.

e. Intramuscular injection usually very painful.

5. Mode of Action: Bacteriostatic

B. *Oleandomycin*, *triacetyloleandomycin* (*Cyclamycin*, *Matromycin*, *TAO*):

These agents have similar activity and there is marked cross-resistance between them and erythromycin as well. Erythromycin is significantly more active than these drugs and since resistance develops relatively easily to any of these agents, the other agents should not be used except under very unusual circumstances where it is demonstrated that an organism is sensitive to one of them and not to erythromycin and another better agent is not available.

Both intrahepatic cholestasis and hepatocellular abnormality occur with triacetyloleandomycin; a significant percentage of patients receiving 1 Gm/day for over two weeks may show such changes. Oleandomycin shows little toxicity.

X. LINCOMYCIN (Lincocin):

1. *Spectrum and Uses*: Active against Gram-positive coccal organisms (including most strains of *S. aureus*) and anaerobes (with the exception of *Bacteroides fragilis*). No activity against *H. influenzae*. Moderate activity vs. *Mycoplasma*.

2. Routes of Administration and Dosage:

a. Oral—0.5-1.0 Gm q 6 h.

b. Intramuscular—600 mg q 12 h.

c. Intravenous—600 mg q 6-8 h.

3. Peak Blood Levels:

a. Oral—3-5 mcg/ml

b. Parenteral—6-13 mcg/ml.

4. Toxicity and Side Effects:

a. Diarrhea.

b. Occasional nausea, emesis or abdominal distress.

- c. Occasional rash or urticaria.
- d. Local reactions to intramuscular injection (inflammation).
- e. Neutropenia—rare, reversible.
- f. Abnormal SGOT levels (occasional).

5. *Miscellaneous*: One-way cross-resistance with erythromycin; strains of *S. aureus* resistant to lincomycin are also resistant to erythromycin.

XI. NOVOBIOCIN (Albamycin):

1. *Spectrum and Uses*: Sometimes useful in *Proteus* (particularly *P. mirabilis* and *P. vulgaris*) infections. Should not be used for pneumococcal or streptococcal infections. Rarely of use in treatment of staphylococcal infections at the present time.

2. *Routes of Administration and Dosage*:

a. Oral—0.25 to 0.5 Gm q 6 h or 0.5-1.0 Gm q 12 h.

b. Intramuscular or intravenous — Same as for oral. *Incompatible with dextrose-containing solutions*. Give slowly intravenously.

3. *Peak Blood Levels*: 20-40 mcg/ml; considerable protein binding.

4. *Toxicity, Side Effects, and Precautions*:

a. Neutropenia—typically mild and reversible. Pancytopenia reported rarely. Hemolytic anemia—rare.

b. Rashes — incidence 10-20%. Occur after 7th to 9th day. May be readily managed with antihistamines as a rule.

c. Urticaria, drug fever, eosinophilia.

d. Appearance of a yellow pigment in the plasma (which may interfere with the determination of serum bilirubin and icteric index) may mask evidence of true liver damage and is therefore an indication for discontinuing the drug.

e. In neonates and young infants, there may be interference with conjugation of bilirubin.

5. *Mode of Action*: Usually bacteriostatic.

6. *Miscellaneous*: There is relatively poor distribution in tissues.

XII. KANAMYCIN - NEOMYCIN - PAROMOMYCIN GROUP:

A. *Kanamycin (Kantrex)*:

1. *Spectrum and Uses*: Safest of group for parenteral administration. Poorly absorbed orally; oral usage is for intestinal infections or for "bowel sterilization." Very effective against a wide variety of Gram-positive and Gram-nega-

tive organisms. Ineffective, or relatively so, against *Pseudomonas*, streptococci, pneumococci, anaerobes, *Brucella*. Some *Klebsiella*-*Aerobacter* strains are resistant. A significant number of *S. aureus* strains at many institutions are extremely resistant. This resistance is high enough to exceed concentrations of drug used topically or achieved in G.I. tract after oral administration.

2. *Routes of Administration and Dosage*:

a. Intramuscular — 15 mg/kg/day or less (usually 1 Gm/day or less). Divided into 2-4 doses.

b. Intravenous — same as intramuscular. Give very slowly. Avoid this route entirely, if possible, particularly in presence of impaired renal function.

c. Oral—1.5 Gm q 4-6 h. Loading dose of 1.0 Gm q h x 4 may be used when rapid effect is desired. Some workers prefer to never exceed 4.0 Gm/day orally.

3. *Peak Blood Levels*:

a. Parenteral—20-35 mcg/ml.

b. Oral—negligible except with severe hepatic disease, renal disease, or in the presence of extensive bowel ulceration.

4. *Toxicity, Side Effects, and Precautions*:

a. Nephrotoxicity—azotemia is chief manifestation. Seen more often in patients with pre-existing impairment of renal function. Recovery slow (4-6 weeks) but apparently complete as judged by the usual clinical determinations. Seen in older patients in absence of obvious evidence of pre-existing impaired renal function.

b. Ototoxicity — both branches of VIII nerve may be involved, but primarily the auditory. Related to dosage, blood level, duration of therapy, impaired renal function (pre-existing or caused by drug), and previous perceptive hearing loss. May occur even with oral therapy in patients with poor renal function, etc. More likely to occur with concomitant or *sequential* use of other ototoxic agents. Essentially irreversible. Observe patients closely for such early evidences of ototoxicity as tinnitus, "fullness" in the ear, and/or audiometric evidence of loss of acuity. Loss of acuity at 4000 and 8000 cycles typically occurs before subjective hearing loss.

c. Pain at injection site occasionally—usually prevented by procaine.

d. Curare-like effect with respiratory paralysis or arrest—may follow intraperitoneal, intrapleural, or rapid intravenous administration, particularly in association with ether anesthesia. Calcium gluconate or neostigmine should be tried as antidotes.

e. Since kanamycin is dialyzable, consideration should be given to utilizing dialysis promptly in patients with early evidence of toxicity.

B. Gentamicin (*Garamycin*):

1. *Spectrum and Uses*: Active against most Gram-negative bacteria including *E. coli*, *Pseudomonas aeruginosa* and *Proteus* species. Kanamycin is more active against *Proteus* species and some strains of *Klebsiella-Enterobacter* but gentamicin is effective against some strains of *Klebsiella-Enterobacter* which are resistant to kanamycin. It is the drug of choice for serious *Pseudomonas* infections, recognizing that occasional strains may be resistant. Its role in the management of staphylococcal infection remains to be defined. It is ineffective against streptococci, pneumococci, and anaerobes.

2. Routes of Administration and Dosage:

a. Intramuscular—0.4-1.0 mg/kg q 8 h. In serious infections, doses of 1.5 mg/kg q 8 h have been used for limited periods.

b. Topical.

3. *Peak Blood Levels*: With normal renal function, doses indicated do not usually produce serum levels in excess of 10 mcg/ml.

4. Toxicity, Side Effects, and Precautions:

a. Similar to that indicated for kanamycin.

b. Ototoxicity—both branches of VIII nerve may be involved, but the vestibular branch is involved more often. Predisposing factors as described under kanamycin probably apply to this drug as well.

C. Neomycin (*Mycifradin*):

1. *Spectrum and Uses*: Very similar to kanamycin. Should not be used parenterally because of greater toxicity. Cross-resistance with other members of group may be seen.

2. Routes of Administration and Dosage:

a. Oral—as with kanamycin.

b. Topical—5 mg/ml or Gm. Caution: large volumes of irrigating fluid or prolonged administration may produce enough absorption to cause toxicity.

3. Peak Blood Levels:

Oral—negligible, except in patients with severe hepatic failure, renal disease, or extensive bowel ulceration.

4. Toxicity, Side Effects, and Precautions:

Qualitatively similar to kanamycin, but more toxic. Here, neostigmine is probably antidote of choice for neuromuscular block. Deafness may progress for extended periods after therapy has been stopped and blood levels are no longer demonstrable.

5. Mode of Action: Bactericidal.

D. Paromomycin (*Humatin*):

Similar to kanamycin and neomycin and shows cross-resistance with them. Used only orally. May be more effective in intestinal amebiasis than related compounds.

XIII. POLYMYXIN-COLISTIN GROUP:

A. Polymyxin B Sulfate (*Aerosporin*):

1. *Spectrum and Uses*: Effective vs. most Gram-negative bacilli other than *Proteus*. Diffuses poorly into body cavities and tissues. Susceptible to inactivation by constituents of cells and tissues. Orally, there is very little absorption so it is useful for some enteric infections.

2. Routes of Administration and Dosage:

a. Intramuscular—2.5 mg/kg body weight/day; give in 3 divided doses (q 8 h). Average dosage is 50 mg q 8 h intramuscularly. May be diluted with procaine.

b. Oral—10-20 mg/kg/day, divided into 4 doses (not absorbed).

c. Intravenous—Same dosage as intramuscular, but never over 200 mg per day. Administer each dose over 60 to 90 minute period.

d. Topical—0.1 to 0.25% concentration.

e. Intrathecal—Treatment of choice for *Pseudomonas meningitis*. 5-10 mg in 10 ml of N/S first day, then 5 mg daily for 3 days, then 5 mg every other day.

3. *Peak Blood Levels*: About 2 mcg/ml.

4. Toxicity, Side Effects, and Precautions:

a. Nephrotoxicity; rising creatinine is indication for lowering dosage or discontinuing drug. Renal shutdown rare. Changes usually reversible, as far as is known.

b. Neurotoxicity—Paresthesias, ataxia, weakness of legs, dizziness. Entirely reversible, but may be disturbing enough to patient to force cessation of treatment.

c. Very painful on injection for most patients.

d. Drug fever.

e. The possibility of neuromuscular blockade with respiratory paralysis should be kept in mind when this agent is used intraperitoneally, intrapleurally, or intravenously. Calcium gluconate counteracts this effect experimentally.

B. *Colistin methanesulfonate (Coly-Mycin)*:

Similar to polymyxin B. Should not be used intravenously or intrathecally (contains dibucaine). Intramuscular dosage—5.0 mg/kg per day in divided doses (q 6 h). Much less pain at intramuscular injection sites. (However, polymyxin given intravenously avoids this problem.) Toxicity comparable to polymyxin B when both are used at full therapeutic dosage. Currently more expensive than polymyxin B.

XIV. VANCOMYCIN (Vancocin):

1. *Spectrum and Uses*: Active against essentially all Gram-positive organisms; ordinarily should be reserved for infections not readily treatable with less toxic agents.

2. *Routes of Administration and Dosage*:

a. Oral — 4 grams/day. Absorption negligible, so useful only for staphylococcal enterocolitis.

b. Intravenous — Parenteral administration must be by the intravenous route. Dosage—2 Gm daily, preferably 1 Gm q 12 h in volume of 50-100 ml administered over 15-30 minutes.

3. *Peak Blood Levels*: 5-20 mcg/ml.

4. *Toxicity, Side Effects, and Precautions*:

a. Thrombophlebitis — less common when given intermittently rather than by constant intravenous drip.

b. Rash, urticaria, drug fever.

c. Anaphylactoid reactions—rare.

d. Nephrotoxicity — particularly in patients with previous impairment of renal function.

e. Ototoxicity—much less frequent than with kanamycin. Related to high blood levels, whether due to impaired renal function or not.

f. Leukopenia (rare).

5. *Mode of Action*: Bactericidal.

6. *Miscellaneous*: It appears to be very difficult to induce resistance to this drug either *in vitro* or *in vivo*.

XV. BACITRACIN:

1. *Spectrum and Uses*: Active against Gram-positive organisms primarily. Rarely used parenterally at present.

2. *Routes of Administration and Dosage*:

a. Parenteral — 50,000 to 100,000 units daily, divided into 4 doses (q 6 h) intramuscularly. Should be diluted in procaine in normal saline. Give *deep* intramuscularly.

b. Intrathecal — 5,000 to 10,000 units in normal saline daily (for staphylococcal meningitis). Very well tolerated by CNS.

c. Topical—500 to 1,000 units/ml or Gm.

3. *Peak blood levels* after parenteral use—0.3 to 3.0 units/ml.

4. *Toxicity, Side Effects, and Precautions*:

a. Pain at injection site.

b. Nephrotoxicity — renal tubular necrosis may occur. If patient's blood urea nitrogen or creatinine is normal and remains so, toxicity will usually be minimal and reversible. Watch urinary output carefully.

5. *Mode of Action*: Bactericidal.

XVI. NITROFURANS:

A. *Nitrofurantoin (Furadantin)*

1. *Spectrum and Uses*: Useful only for urinary tract infections. Most urinary tract infections with *E. coli*, staphylococci and enterococci respond. About 50% of infections due to *Proteus* species or *Klebsiella-Enterobacter* respond. *Pseudomonas* is resistant and may cause superinfection.

2. *Routes of Administration and Dosage*:

a. Oral—50-100 mg q 6 h.

b. Intravenous (Furadantin sodium)—180 mg in 500 ml of diluent q 12 h (60 drops/minute). Reduce dosage for patients under 120 lbs. Dissolve crystals just prior to use.

3. *Blood Levels*: Negligible.

4. *Toxicity, Side Effects, and Precautions*:

a. Nausea, vomiting—minimized by taking drug with food.

b. Headache, malaise, dizziness.

c. Rash, urticaria, other sensitivity reactions (including pulmonary infiltrates).

d. Hemolytic anemia in certain susceptible patients (people with red cells having glucose-6-phosphate dehydrogenase deficiency).

e. Peripheral neuritis — particularly in patients with impaired renal function or predisposition to neuritis (diabetes, avitaminosis, etc.).

5. *Mode of Action*: Primarily bacteriostatic.

6. *Miscellaneous*: Macrodantin is a macrocrystalline form of nitrofurantoin which is probably comparable in activity and which may offer the advantage of fewer gastrointestinal side effects.

B. *Furazolidone (Furoxone)*:

1. *Spectrum and Uses*: This nitrofurantoin is used for treatment of enteric disease due to *Shigella* and *Giardia*.

2. *Route of Administration and Dosage*: 100 mgm orally q 6 h.

3. *Toxicity, Side Effects, and Precautions*:

a. Reactions similar to those described for nitrofurantoin.

b. Disulfiram-like reactions may occur after alcohol in patients on this drug.

c. Urine may turn brown (not a sign of toxicity).

4. *Blood Levels*: Drug absorbed poorly; blood levels very low.

XVII. NALIDIXIC ACID (NegGram):

1. *Spectrum and Uses*: Useful primarily for urinary tract infections. May be useful in therapy of *Shigella* and enteropathogenic *E. coli* enteritis and the *Salmonella* carrier state, but available studies are not adequate to allow one to properly judge its place in the management of these conditions. In the case of urinary tract infection, it is most useful against *Proteus* but may also be useful in infections due to *E. coli*, *Klebsiella-Enterobacter* and occasionally strains of *Pseudomonas*, staphylococci and enterococci.

2. *Routes of Administration and Dosage*: Available only for oral use. The usual initial dose is 4.0 Gm/day given in four divided doses. If therapy is continued for longer than 7-10 days, dosage should be reduced to 2.0 Gm/day.

3. *Toxicity, Side Effects, and Precautions*:

a. Nausea, emesis, occasionally diarrhea.

b. Rash, urticaria, drug fever, eosinophilia, photosensitivity.

c. Occasional elevation of SGOT.

d. Occasional neural disturbances — headache, drowsiness, dizziness, visual disturbances, acute toxic psychosis, convulsions.

XVIII. AMPHOTERICIN B (Fungizone):

1. *Spectrum and Uses*: Effective against both North and South American blastomycosis, histoplasmosis, moniliasis, sporotrichosis, cryptococcosis (torulosis), aspergillosis, mucormycosis and coccidioidomycosis.

2. *Routes of Administration and Dosage*:

a. Intravenous — Start with daily dose of 5 mg and increase gradually (by 5-10 mg/day) to maintain dosage of 50-70 mg every other day. Drug must be administered in 5% dextrose in water using 100 to 150 ml of solution for each 10 mg of drug. Administer over not less than 6 hour period, using small gauge needle. Analgesics, antihistamines, sedatives, etc. may be used to minimize reactions. Total dosage should not exceed 2.0-3.0 Gm, if possible.

b. Intrathecal or intraventricular* — Dilute drug in sterile distilled water to a concentration of 0.25 mg/ml. The initial dose should not exceed 0.1 mg. This should be administered slowly after first diluting solution with 6-8 volumes of spinal fluid. Increase dosage at rate of 0.1 mg for each subsequent injection to maximum of 0.5-0.7 mg. Solutions must be made fresh each time. Injections should be given 3-4 x weekly, preferably alternating between lumbar and cisternal sites after the first few lumbar injections. Ordinarily, this schedule is followed for approximately one month and then maintenance injections of 0.5 mg are given intracisternally once weekly for at least two more months. Intraventricular therapy may be used in place of lumbar or cisternal intrathecal therapy.

c. Topical—Amphotericin may also be used locally in the pleural space, joints, directly into superficial lesions, etc., in selected cases.

3. *Toxicity, Side Effects, and Precautions*:

a. Fever, chills, headache, nausea, vomiting.

b. Phlebitis.

c. Anemia; requires transfusion at times.

d. Nephrotoxicity—Unique nephropathy involving hyperkalemia, nephrocalcinosis and other features suggestive of renal tubular acidosis. Decreased glomerular perfusion is another feature. Renal toxicity probably best followed by endogenous creatinine clearance.

e. Arachnoiditis may follow intrathecal therapy.

*Repeated intraventricular injection is feasible only when a device such as an Ommaya valve has been implanted surgically.

DRUGS OF CHOICE FOR SPECIFIC BACTERIA

SYDNEY M. FINEGOLD, M.D., AND ALVIN DAVIS, M.D.

The choices below are not necessarily appropriate for urinary tract infection. See sections on sulfonamides, oral penicillin G, nitrofurantoin and

nalidixic acid for information concerning the use of these agents in urinary tract infections.

All the drugs effective against a given organism are not necessarily listed. Drugs listed first are usually the most effective or least toxic, or both. Italicized drugs are outstanding in effectiveness against the particular organism.

GRAM-NEGATIVE BACILLI

<i>Organism</i>	<i>Drug of Choice</i>
<i>Achromobacter anitratus</i>	Kanamycin, polymyxin or colistin, tetracycline, erythromycin
<i>Achromobacter lwoffii</i>	Tetracycline, kanamycin, polymyxin or colistin, erythromycin, chloramphenicol
<i>Achromobacter</i> —other species	Polymyxin or colistin, kanamycin, tetracycline, chloramphenicol
<i>Actinobacillus actinomycetemcomitans</i>	Tetracycline, streptomycin, chloramphenicol, ? ampicillin, ? penicillin
<i>Actinobacillus lignieresii</i>	Kanamycin, ? polymyxin or colistin
<i>Aeromonas hydrophila</i>	Tetracycline, kanamycin, chloramphenicol
Arizona	Ampicillin, cephalothin, tetracycline, chloramphenicol
<i>Bacteroides fragilis</i>	Tetracycline, chloramphenicol, erythromycin, lincomycin, penicillin
<i>Bacteroides melaninogenicus</i>	<i>Penicillin</i> , lincomycin, tetracycline, chloramphenicol
<i>Bartonella bacilliformis</i>	Penicillin C, chloramphenicol, streptomycin, tetracycline
<i>Bordetella pertussis</i>	Ampicillin, tetracycline
<i>Brucella</i>	Tetracycline, chloramphenicol
<i>Calymmatobacterium granulomatis</i>	Tetracycline, streptomycin, chloramphenicol
<i>Chromobacterium</i>	Streptomycin, tetracycline, chloramphenicol
<i>Citrobacter</i>	Polymyxin or colistin, kanamycin, chloramphenicol, tetracycline
<i>E. coli</i>	Chloramphenicol, tetracycline, kanamycin, gentamicin, ampicillin, cephalothin, polymyxin
<i>Edwardsiella</i>	Tetracycline, chloramphenicol, polymyxin or colistin, ampicillin
Enterobacter — Subgroup A (<i>Aerobacter cloacae</i>)	} Gentamicin, kanamycin, polymyxin or colistin
Enterobacter — Subgroup B (<i>Aerobacter aerogenes</i>)	
Enterobacter — Subgroup C (<i>Aerobacter liquefaciens</i>)	
<i>Flavobacterium</i>	Chloramphenicol, sulfadiazine
<i>Fusobacterium</i> (<i>fusiform bacilli</i>)	<i>Penicillin</i> , lincomycin, tetracycline, chloramphenicol
<i>Hafnia</i>	Tetracycline, chloramphenicol, kanamycin
<i>Hemophilus aphrophilus</i>	Ampicillin, tetracycline, chloramphenicol, streptomycin
<i>Hemophilus ducreyi</i>	Tetracycline, sulfonamides, chloramphenicol, streptomycin
<i>Hemophilus influenzae</i>	Tetracycline, chloramphenicol, streptomycin, kanamycin, penicillin
<i>Klebsiella pneumoniae</i>	Gentamicin, kanamycin, polymyxin or colistin
<i>Klebsiella rhinoscleromatis</i>	Streptomycin, tetracycline, chloramphenicol
<i>Moraxella liquefaciens</i>	Penicillin, ampicillin, chloramphenicol, tetracycline
<i>Moraxella duplex</i> , var. <i>nonliquefaciens</i>	Penicillin, tetracycline, kanamycin
<i>Pasteurella multocida</i> (<i>septica</i>)	<i>Penicillin</i> , tetracycline, chloramphenicol
<i>Pasteurella pestis</i>	Streptomycin plus either tetracycline or chloramphenicol
<i>Pasteurella pseudotuberculosis</i>	Tetracycline, ? chloramphenicol, ? streptomycin
<i>Pasteurella</i> (<i>Francisella</i>) <i>tularensis</i>	Streptomycin plus either tetracycline or chloramphenicol
<i>Proteus mirabilis</i>	Kanamycin, ampicillin, cephalothin or cephaloridine, chloramphenicol, penicillin, gentamicin

Organism	Drug of Choice
<i>Proteus morganii</i>	Kanamycin, chloramphenicol, gentamicin
<i>Proteus rettgeri</i>	Kanamycin, gentamicin
<i>Proteus vulgaris</i>	Kanamycin, chloramphenicol, gentamicin
<i>Providencia</i>	Kanamycin, chloramphenicol, tetracycline, polymyxin or colistin
<i>Pseudomonas aeruginosa</i>	Gentamicin, polymyxin or colistin, oxytetracycline, chloramphenicol
<i>Pseudomonas maltophilia</i>	Polymyxin or colistin, chloramphenicol, kanamycin
<i>Pseudomonas pseudomallei</i>	Chloramphenicol, kanamycin, sulfadiazine, tetracycline
<i>Pseudomonas stutzeri</i>	Ampicillin, cephalothin, kanamycin, polymyxin or colistin
<i>Salmonella typhi</i>	Chloramphenicol, ampicillin
<i>Salmonella</i> , other than <i>S. typhi</i>	Chloramphenicol, ampicillin, cephalothin
<i>Serratia marcescens</i>	Gentamicin, kanamycin, chloramphenicol
<i>Shigella</i>	Ampicillin, cephalothin, kanamycin, tetracycline, chloramphenicol
<i>Sphaerophorus necrophorus</i> (<i>Bacteroides funduliformis</i>)	Tetracycline, chloramphenicol, penicillin, lincomycin
<i>Streptobacillus moniliformis</i>	Penicillin
<i>Vibrio cholerae</i>	Tetracycline, chloramphenicol
<i>Vibrio fetus</i>	Tetracycline, chloramphenicol, ampicillin, streptomycin

GRAM-NEGATIVE COCCI

<i>Gonococcus</i> (<i>Neisseria gonorrhoeae</i>)	Penicillin, tetracycline, erythromycin
<i>Meningococcus</i> (<i>Neisseria meningitidis</i>)	Penicillin, ampicillin, chloramphenicol, erythromycin, tetracycline, sulfadiazine

GRAM-POSITIVE BACILLI

<i>Actinomyces israelii</i>	Penicillin, tetracycline, chloramphenicol, cephalothin
<i>Bacillus anthracis</i>	Penicillin, erythromycin, tetracycline
<i>Clostridium</i>	Penicillin, tetracycline, chloramphenicol
<i>Corynebacterium acnes</i>	Tetracycline, ? lincomycin
<i>Corynebacterium diphtheriae</i>	Penicillin, erythromycin, cephalothin
<i>Corynebacterium</i> , other	Vancomycin, penicillin, erythromycin
<i>Erysipelothrix rhusiopathiae</i>	Penicillin, ? tetracycline
<i>Listeria monocytogenes</i>	Tetracycline, ampicillin, penicillin, erythromycin
<i>Nocardia</i>	Sulfonamides, cycloserine

GRAM-POSITIVE COCCI

<i>Pneumococcus</i> (<i>Diplococcus pneumoniae</i>)	Penicillin, erythromycin
<i>Staphylococcus</i>	Methicillin, cloxacillin or dicloxacillin, cephalothin or cephaloridine, nafcillin, vancomycin, lincomycin

Streptococci

Aerobic and microaerophilic strep.

(and cocci)	Penicillin, lincomycin, erythromycin, chloramphenicol, vancomycin
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Enterococci	Penicillin plus streptomycin, chloramphenicol, vancomycin, penicillin plus kanamycin, ampicillin, (tetracycline for <i>S. liquefaciens</i>)
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Group A beta-hemolytic strep.	Penicillin, erythromycin, ampicillin, cephalothin
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Viridans group	Penicillin, vancomycin, cephalothin
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SPIROCHETES

<i>Borrelia recurrentis</i>	Tetracycline, chloramphenicol, penicillin
<i>Spirillum minus</i>	Penicillin, erythromycin
<i>Treponema pallidum</i>	Penicillin, erythromycin, tetracycline

RICKETTSIAE, MYCOPLASMA, CHLAMYDIA (BEDSONIA)

<i>Rickettsia</i>	Tetracycline, chloramphenicol
<i>Mycoplasma pneumoniae</i>	Tetracycline, erythromycin
<i>Psittacosis</i> (ornithosis)	Tetracycline, chloramphenicol
<i>Lymphogranuloma venereum</i>	Tetracycline, chloramphenicol, sulfonamides

INVESTIGATIONAL ANTIMICROBIAL AGENTS

ALVIN DAVIS, M.D.

The antimicrobial agents described below have not been approved for general use by the Food and Drug Administration as of the time of this publication. With one exception (saramycetin), they have been available to investigators in significant quantities for purpose of evaluation so that considerable data are usually available. However, the information presented may not prove to be entirely accurate as additional experience is acquired and reported.

Carbenicillin

Carbenicillin is the disodium salt of carboxybenzyl penicillin, a semi-synthetic penicillin. It is a bactericidal drug which is excreted rapidly unchanged into the urine.

Antimicrobial Activity—Carbenicillin is active against Gram positive organisms such as staphylococci, streptococci, and pneumococci, but its uniqueness is referable to its activity against Gram negative organisms not ordinarily susceptible to any other penicillin. It is active against some strains of *Pseudomonas aeruginosa*, *Proteus morgani*, *Proteus rettgeri* and *Proteus vulgaris*. It is also active against *Hemophilus influenza*, and about as active as ampicillin against *Escherichia coli*, *Proteus mirabilis*, and *Shigella* species. It is inactivated by staphylococcal beta lactamase. Because of the variability of susceptibility to this drug of the resistant Gram negative organisms, in vitro susceptibility tests are important in the rational use of this drug.

Dosage and Administration—Carbenicillin is suitable for intravenous or intramuscular administration. There is no oral preparation. Dosage depends upon severity of the infection and the susceptibility of the etiologic agent to the drug. Minimum dose is usually 1 gram every six hours, but doses of 30 grams per day of carbenicillin in addition to probenecid may be administered in severe or resistant infection. Carbenicillin may be administered intrathecally or intraventricularly in doses of 40 mg daily to patients with meningitis. High doses need not be used in urinary infection because approximately 70% of the drug appears in the urine within five hours after intramuscular administration.

Toxicity and Side Effects—Patients known to be allergic to any penicillin may manifest an allergic response to this drug. There are no known toxic effects produced by the drug.

Cephaloglycin

Cephaloglycin is a phenyl glycine analog of the antibiotic cephalothin suitable for oral use. It is a zwitterion and therefore contains no cation. It is bactericidal in its activity.

Antimicrobial Activity—In general, it is as active against Gram negative organisms as are cephalothin and cephaloridine. It is less active than cephaloridine against staphylococci. Because of in vitro instability of cephaloglycin, in vitro testing may be misleading unless it is recognized that both tube dilution and disc susceptibility tests may be in error because of inactivation of the drug and the subsequent growth of susceptible organisms. In addition, because of low serum levels achieved, susceptibility to low concentrations of the drug would have to be assured for treatment of infections other than those of the urinary tract.

Dosage and Administration—Tentative dosage range is 250 mg to 1 gram by mouth four times daily, preferably on an empty stomach. Peak serum levels two hours after a single 500 mg dose taken in the fasting state were between 2 and 3 mcg/ml. Urine concentrations after the same dose were usually greater than 300 mcg/ml.

Toxicity and Side Effects—The possibility of renal toxicity is suggested by animal toxicity studies which used large parenteral or intraperitoneal doses. This has not been observed in animals or humans to whom the drug has been administered by mouth. Allergic reactions may be expected in patients allergic to other cephalosporin C derivatives, and perhaps in patients allergic to penicillin as well.

Cephalexin

Cephalexin is a desacetoxy analog of the antibiotic cephaloglycin. It is a zwitterion and is bactericidal against susceptible strains. Its chief advantage is better absorption on oral administration, with resulting high serum levels.

Antimicrobial Activity—It is active against both Gram-negative and Gram-positive organisms susceptible to other cephalosporin derivatives. Although it appears to be less active on a weight basis against certain organisms than other cepha-

losporin derivatives, this effect is offset by the high serum levels achievable with therapeutic doses. There is evidence that some strains of *S. aureus* may develop resistance to the drug. There is not yet sufficient data to assess the extent or importance of this phenomenon.

Dosage and Administration—Tentative adult dosage is 250 to 500 mg three to four times daily. Food in the stomach interferes with absorption. A single 500 mg dose taken in the fasting state produced an average peak serum level of 18 mcg/ml in 12 adults. Approximately 70-80% of the drug is excreted unchanged into the urine within four hours of oral administration on an empty stomach.

Toxicity and Side Effects—There is little data on toxicity, but it appears that increased frequency of bowel movements or diarrhea may occur. There is no information concerning possible nephrotoxicity in clinical usage. Allergy to other cephalosporin derivatives, and perhaps to penicillin as well, may make allergic response to cephalexin likely.

Rifampicin (Rifampin)

Rifampicin (rifampin) is the amino methyl piperazine derivative of rifamycin S.V. The naturally occurring rifamycins from which this drug is derived were first isolated from cultures of *Streptomyces mediterranei* in 1959. It is unrelated chemically to other commonly available antibiotics. The mechanism of action is not fully understood but there is no evidence that it interferes with the synthesis of either cell wall, protein or nucleic acid. Unlike the parent rifamycin S.V., rifampicin is effective orally.

Antimicrobial Activity—The minimum inhibitory concentrations (MIC) for most strains of *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Diplococcus pneumoniae* are very low (<0.5 mcg/ml). The MIC for Gram-negative pathogens and for enterococcus is higher but many strains are inhibited by 10 mcg/ml or less. The manufacturer is presently restricting investigational use to therapy of mycobacterial and gonococcal infections. All strains of *M. tuberculosis var. hominis* examined were inhibited by levels of 1 mcg/ml or less. Atypical mycobacteria are also often susceptible.

The significance of a potential problem of early development of resistance on the part of some microorganisms remains to be determined.

Dosage and Administration—Rifampicin is available for oral use only. The usual adult dose is 300 mg tid, preferably on an empty stomach. A peak level of 3 to 5 mcg/ml is reached two to three hours after a single 300 mg dose and the level at 12 hours is not measurable. The drug is excreted primarily into the bile, but ten percent to 15 percent is recovered in the urine.

Toxicity and Side Effects—Granulocytopenia (apparently reversible) has been reported. Rarely, mild headache and gastrointestinal complaints have been observed.

Saramycetin

Saramycetin is an anti-fungal drug which has been known previously by the code designations RO 2-7758 and X-5079C. It is a polypeptide produced by a species of *Streptomyces*. Technical difficulties have limited the availability of this drug markedly despite the length of time it has been known.

Antimicrobial Activity—This drug appears to have a clinically useful level of activity for the treatment of infections caused by *Blastomyces dermatitidis* and *Histoplasma capsulatum*, and to a lesser extent *Sporotrichum schenkii*. Activity against *Coccidioides immitis* is of questionable usefulness, and it is ineffective in *Cryptococcus neoformans* infections.

Dosage and Administration—Usual dose reported is 3 to 5 mg/kg/day subcutaneously for periods of four to six weeks.

Toxicity and Side Effects—Alteration in liver function tests was almost universal in patients treated. Results of liver function tests usually returned to normal in patients without pre-treatment abnormalities of liver function. Pre- and post-treatment liver biopsies have shown variable tissue changes. Other side effects of treatment that have been observed are eosinophilia, local pain and inflammation at injection site, febrile reactions and urticarial reactions.

ANTIBACTERIAL AGENTS IN RENAL INSUFFICIENCY

IRWIN ZIMENT, M.B., M.R.C.P.

1. Excretion of Antibacterial Agents:

Most antibiotics and chemotherapeutic agents, and their degradation products, are excreted mainly by the kidneys, thus necessitating reduc-

TABLE 1.—*Dosage Modifications Required in Renal Insufficiency.*
(*Tabulation of the antibacterial agents on the basis of renal and extra-renal toxicity as determinants for dosage modification in renal insufficiency.*)

MAJOR MODIFICATION			MINOR MODIFICATION	NO MODIFICATION	CONTRA-INDICATED
<i>Major Renal Toxicity</i>		<i>? Renal Toxicity</i>	<i>No Renal Toxicity</i>		
<i>Major Extra-Renal Toxicity</i>	<i>Minor or No Extra-Renal Toxicity</i>	<i>Major Extra-Renal Toxicity</i>	<i>Some Extra-Renal Toxicity</i>	<i>(Avoid High Dosage)</i>	
Kanamycin Gentamicin Neomycin† Vancomycin Amphotericin (? Short-acting sulfonamides)	Polymyxin Colistin Bacitracin† Cephaloridine†	Streptomycin Tetracycline* Oxytetracycline* Chlortetracycline*	Chloramphenicol Lincomycin** Cephalothin** INH PAS† Cycloserine (? Ethambutol)	Penicillin‡ Ampicillin Methicillin*** Other penicillins Erythromycin Novobiocin	Nitrofurantoin Nalidixic acid Methenamine Long-acting sulfonamides Long-acting tetracyclines

*Intravenous tetracycline causes higher peak blood levels and such therapy is more hazardous than oral dosage. Particular caution should be observed in pregnant women. Out-dated tetracycline products should never be used, since rare cases of the Fanconi syndrome have resulted; this occurred particularly under moist storage circumstances in products containing citric acid in the formulation. Chlortetracycline is rarely used now.

**Cephalothin and lincomycin do not appear to be toxic in renal failure, but lower dosage is recommended since retention of the drugs occurs, making usual dosage regimens excessive.

***Methicillin has caused hypersensitivity nephrotoxic reactions. Large dose therapy can introduce an appreciable sodium load, which could be dangerous in renal failure.

†These agents should be avoided in uremic patients.

‡Large dose penicillin therapy in renal failure can introduce a dangerous electrolyte load, and also carries a marked risk of neurotoxicity.

tion of dosage in patients with renal insufficiency. This is important not only in the case of nephrotoxic drugs, but also for those drugs which have major extrarenal toxicity. Reduced dosage is also desirable for most non-toxic antibacterial agents which are cleared by the kidney, since normal dosage would produce accumulation in the body, whereas lower dosage regimens offer advantages in economy and ease of administration with less risk of superinfection.

The appropriate dosage to administer is based upon whether or not the drug is excreted by the kidney:

(1) *Cleared mainly by the kidney:*

(a) *Major nephrotoxic agents:* kanamycin, neomycin, gentamicin, polymyxin, colistimethate, vancomycin, cephaloridine, sulfonamides, amphotericin, bacitracin

(b) *Possibly nephrotoxic agents:* tetracycline, streptomycin

(c) *Non-nephrotoxic agents* (in usual dosage):

(i) No extra-renal toxicity: penicillin, methicillin, ampicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin, cephalothin, lincomycin

(ii) Some extra-renal toxicity: INH, PAS

(2) *Not cleared by kidney* (in unchanged form):

(a) *Potentially toxic:* chlortetracycline, chloramphenicol

(b) *Non-toxic:* erythromycin, novobiocin

For dosage modifications see Tables 1 and 2.

2. Antibacterial Agents Contraindicated in Renal Failure:

a. *The antituberculosis drugs* — Pyrazinamide, ethionamide, cycloserine, viomycin and ethambutol are best avoided in patients with marked renal impairment. Only viomycin is nephrotoxic, but the others all have marked extrarenal toxicity. No dosage schedule for use of these second-line drugs in renal failure can be recommended as safe since information in this area is inadequate; only INH, streptomycin, PAS, and possibly ethambutol and cycloserine should be used. INH appears to be very safe in azotemia unless the patient is malnourished or alcoholic; in such cases reduced INH dosage with pyridoxine supplements is advisable. Many uremic patients have difficulty tolerating PAS, and unless its use is considered to be essential, it should be avoided in severe renal insufficiency. Streptomycin should be used with appropriate dosage reduction in uremia; elderly patients are particularly liable to suffer toxic effects, and should be carefully monitored.

b. *Agents used for urinary tract infections—*

(1) *Sulfonamides* should not be used in patients who cannot maintain adequate fluid intake or when renal insufficiency is present. The dangers of crystalluria and extra-renal toxicity make these drugs unsuitable, unless therapy can be carefully controlled.

(2) *Nitrofurantoin* and *nalidixic acid* are

TABLE 2.—Antibiotic Dosage in Renal Failure

Antibiotic	Normal-36% Normal Renal Function (Normal Creatinine)	35%-10% Normal Renal Function (Creatinine 1.5-5.0)	9%-0% (Anuria) of Renal Function (Creatinine > 5.0)
Aq. Penicillin G	Normal dose depending on infection	Normal dose, but high dosage therapy contraindicated	
Ampicillin	Normal dose depending on infection	Normal dose	Normal dose
Oxacillin (IM or IV)	Normal dose depending on infection	Normal dose	0.25-1.0 Gm q 6 h
Cloxacillin (oral)	Normal dose depending on infection	Normal dose	0.25-0.5 Gm q 6 h
Dicloxacillin	Normal dose depending on infection	Normal dose	0.25-0.5 Gm q 6 h
Methicillin	1.0-3.0 Gm q 3-6 h	1.0-2.0 Gm q 3-6 h	1.0-2.0 Gm q 4-8 h
Nafcillin	0.25-3.0 Gm q 3-6 h	0.25-1.0 Gm q 3-6 h	0.25-1.0 Gm q 3-6 h
Cephalothin	1.0-3.0 Gm q 3-6 h	1.0-2.0 Gm q 6-8 h	1.0 Gm q 6-24 h
Cephaloridine	0.25-1.0 Gm q 6 h	Do not use	Do not use
Lincomycin (oral)	0.5 Gm q 6-8 h	0.25 Gm q 6-8 h	0.25 Gm q 8-12 h
Lincomycin (IM, IV)	0.6 Gm q 8-12 h	0.3 Gm q 8-12 h	0.2 Gm q 8-12 h
Erythromycin	0.25-0.5 Gm q 6 h	0.25-0.5 Gm q 6 h	0.25-0.5 Gm q 6 h
Novobiocin	0.25-0.5 Gm q 6 h	0.25-0.5 Gm q 6 h	0.25-0.5 Gm q 6 h
Tetracycline and Oxytetracycline (oral)	0.25-0.5 Gm q 6 h	1st day: 0.25 Gm q 6 h Then: 0.5 Gm q 1-2 days	1st day: 0.25 Gm q 6 h Then: 0.5 Gm q 3-4 days
Chlortetracycline (oral)	0.25-0.5 Gm q 6 h	0.25-0.5 Gm q 6 h	(do not give intravenously) Use not advised
Chloramphenicol	0.25-1.0 Gm q 6 h	0.25-1.0 Gm q 6 h	(?) Normal dose
INH	300 mg q.d. (in 1 dose)	100 mg q 8 h + pyridoxine	(?) 100 mg qd + pyridoxine
PAS	4 Gm t.i.d.	2 Gm t.i.d.	Do not use
Neomycin (oral)	1.5 Gm q 4-6 h	Do not use	Do not use
Kanamycin (oral)	1.5 Gm q 4-6 h	1.0 Gm q 8-12h	Do not use
Kanamycin (I.M.)	7.5 mg/kg/day q12h	1st day: 7.5 mg/kg q12h (x2) Then 7.5 mg/kg q1-2 days	1st day: 7.5 mg/kg (1 dose only) Then: 7.5 mg/kg q3-6 days
Streptomycin	0.5-1.0 Gm q12h	1st day: 0.5 Gm q12h (x2) Then 0.5 Gm q1-2 days	1st day: 0.5 Gm q12h (x2) Then: 0.5 Gm q3-4 days
Vancomycin	1 Gm q12h	0.5 Gm q2-3 days	1.0 Gm q10 days
Polymyxin (I.M., I.V.)	0.8 mg/kg q8h	1st day: normal dosage Then: 0.8 mg/kg q48h	1st day: normal dosage Then: 0.8 mg/kg q3d
Colistimethrate (I.M.)	1.6 mg/kg q8h	1st day: normal dosage Then: 1.6 mg/kg q36-38h	1st day: normal dosage Then: 1.6 mg/kg q3d
Gentamicin (I.M.)	0.3-1.5 mg/kg q8h-q12h	1st day: normal dosage Then: 0.3-1.0 mg/kg q12-24h	1st day: normal dosage Then: 0.3-1.0 mg/kg q3-4 days
Nitrofurantoin (oral)	100 mg q6h	Do not use	Do not use
Nitrofurantoin (I.V.)	180 mg q12h	Do not use	Do not use
Nalidixic acid	0.5-1.0 Gm q6h	Do not use	Do not use
Sulfonamides	Normal dose	Do not use	Do not use
Methenamine	1.0 Gm q6h (+ urine acidification to pH 5.0-5.5)	Do not use	Do not use
Amphotericin	1.0 mg/kg 3 x/week (Dosage depends on effect on creatinine clearance)	1.0 mg/kg 2 x/week	Unknown

specifically indicated for the treatment of urinary tract infections, but are only effective when renal function is normal, and should not be used otherwise since extra-renal toxicity may result.

(3) *Methenamine* is only effective in the treatment of urinary tract infections when the urine pH is reduced to 5-5.5 (e.g. by giving methionine). Acidification of the urine in renal failure may prove impossible, and systemic

acidosis can result from giving acidifying drugs. Therefore, methenamine, although relatively non-toxic, is unsuitable for patients with renal insufficiency.

3. Principle in the Treatment of Infections in the Presence of Renal Insufficiency:

(1) The least nephrotoxic agent should always be selected, (preferably on the basis of bacteriologic susceptibility studies).

(2) A relatively non-toxic (all types of toxicity

considered) antibiotic should be given if suitable; e.g., penicillin G, ampicillin, penicillinase-resistant penicillins, erythromycin, cephalothin.

(3) A toxic agent should be given for as short a period as is consistent with effective eradication of the infection.

(4) Frequent serum creatinine levels and creatinine clearance, if possible, should be obtained to guide changes in drug dosage. Urine output should be watched.

(5) The patient's clinical response is as important a guide to dosage as are the recommendations in Table 2.

(6) Avoid long-acting preparations of penicillins, tetracyclines, sulfonamides or other drugs.

(7) *Chlortetracycline* is more readily inactivated than other tetracyclines. However, it may have a catabolic effect and therefore its use in the presence of azotemia is no longer advised.

(8) *Chloramphenicol* degradation products could accumulate in patients with renal insufficiency; it is still not clear whether or not these metabolites are toxic.

(9) *Sulfonamides* may present an added risk to the patient with renal insufficiency, although one study suggests that sulfadimidine is not retained and is effective therapy for urinary infections in the presence of azotemia.

(10) *Amphotericin* therapy induces renal defects in most recipients; while these are initially reversible, long-term intravenous administration often causes permanent damage, and a loss in renal function may have to be accepted if the fungal infection is to be effectively treated. The modification of dosage which may be necessary in patients with renal insufficiency is unknown.

4. Nephrotoxic Antibiotics in Renal Failure:

Severe infections in patients with renal failure may necessitate therapy with nephrotoxic agents, and the risk of further deterioration in renal function must be balanced against the dangers of the infection. Renal function may actually be improved if the infection is in the kidneys or if there is pre-renal failure associated with systemic infection.

If the patient has end-stage renal disease, the further damage that may occur while using a nephrotoxic agent is relatively unimportant if the patient can subsequently be admitted to a chronic dialysis program. This applies in particular to the use of polymyxin or colistimethate whose extra-renal toxicity is not a major problem; however, high blood levels of these drugs may produce

apnea (the other neurotoxic effects of the polymyxins are always reversible). Cephaloridine and bacitracin (which is rarely used) are likewise nephrotoxic, but differ from the polymyxins in having no extra-renal toxicity, and theoretically may be safely used in irreversible renal failure, whereas they should not be used if there is hope of renal improvement.

5. Treatment of Urinary Tract Infections:

This usually proves to be unsatisfactory in patients with chronic renal failure since the concentration of antibiotics in the urine, and possibly in the renal parenchyma, is generally inadequate. Treatment with the largest recommended dosage of the less toxic antibiotics should be tried, with repeated urine culture as a guide to the success of therapy.

It is of interest that the combination of penicillin or ampicillin with a penicillinase-resistant penicillin may occasionally give a synergistic bactericidal effect against a wide spectrum of bacteria including *Pseudomonas*. A return of infection is usual after antibacterial therapy is terminated, however.

It is important to remember that the effectiveness of many antibacterial agents may be very dependent upon the pH of the medium:

(1) *More effective in alkaline urine:* erythromycin, streptomycin, kanamycin, gentamicin, sulfonamides.

(2) *More effective in acid urine:* tetracyclines, novobiocin, cycloserine, nitrofurantoin, methenamine compounds.

(3) *Relatively independent of pH:* chloramphenicol, ampicillin, (?) polymyxins.

In the presence of renal insufficiency, attempts to alter the urinary pH may not be possible without serious changes in acid-base balance.

6. Evaluation of Renal Function:

The serum creatinine provides a good guide to renal status, and serial endogenous creatinine clearances provide the best guide to changes in renal function when using a nephrotoxic antibiotic. Even a barely elevated serum creatinine is consistent with a 75 percent loss of renal function. Restriction in dosage of drugs cleared by the kidney is required only when renal function is less than 35 percent normal. An initial creatinine determination should always be obtained prior to starting therapy with a nephrotoxic antibiotic and frequent creatinine determinations should be obtained during therapy, even in patients with no

known renal disease. Urine examination is not so helpful, since an abnormal sediment may appear during therapy without any significant damage to the kidney having occurred.

7. Extra-renal Toxicity of Antibacterial Agents:

The non-renal toxic effects of kanamycin, vancomycin, streptomycin, tetracyclines (especially intravenous), and possibly chloramphenicol and INH are an increased hazard when renal function is borderline. Monitoring of serum creatinine safeguards against inadvertent accumulation of these drugs when renal function is suspect. Kanamycin is a particular danger since rapid onset of hearing loss has followed in some patients with overdosage; single dose therapy with this drug should not exceed 7.5 mg/kg since deafness has been recorded after a single dose of 1 Gm in a patient with renal impairment.

8. Antibiotic Serum Assays:

These are rarely performed by routine hospital laboratories, but should be helpful in patients with renal failure who are receiving potentially toxic agents. This applies both to nephrotoxic agents and to those with major toxicity in other areas.

It is unfortunate that such exact guidance can rarely be employed, since reliable and meaningful results can only be obtained from laboratories which do assays regularly. Further, assays take time, and the delayed results may not help in a critical case.

The therapeutic range for an antibiotic depends upon the particular infection and the toxic level is not always known. The following levels should prove therapeutically adequate, and should not be exceeded if toxic effects are to be avoided. (Blood samples should be taken about two hours after administering the drug):

Streptomycin 20-40 mcg/ml
Chloramphenicol 15-30 mcg/ml
Kanamycin 10-20 mcg/ml
Vancomycin 10-20 mcg/ml
Colistin 10-20 mcg/ml
Gentamicin 7-10 mcg/ml
Polymyxin 5-10 mcg/ml
Tetracycline 3-10 mcg/ml
INH 1-3 mcg/ml

It may also be useful to check the levels at periods of 24 hours after drug doses for a guide to possible adjustment in frequency of administration. When treating a urinary tract infection in renal insufficiency it may be useful to assay the urine to ensure that adequate amounts of the agent do get

excreted. If insufficient amounts are excreted, then administering the agent may prove futile and introduces an unnecessary hazard. Assays of antibiotics in urine are simpler to perform than are serum assays.

9. Recovery Phase Following Acute Renal Failure:

The diuretic phase following acute renal shutdown is associated with persistence of the impairment of excretory function. Normal dosage of those antibiotics excreted principally by the kidney remains hazardous until the creatinine clearance has returned to normal. For practical purposes a creatinine clearance of less than 10 ml/min implies anuria.

10. Hepatorenal Failure:

The association of hepatic failure with renal insufficiency necessitates further reduction in dosage of certain of those antibiotics excreted or inactivated by the liver, i.e. ampicillin, tetracycline group, chloramphenicol, erythromycin (estolate), novobiocin, lincomycin and possibly cephalothin. In managing hepatorenal failure oral kanamycin is safer than neomycin, but either may accumulate to reach toxic levels in the blood. For further details see section on Antibiotics and Liver Disease.

11. Use of Antibacterial Agents in Patients on Dialysis:

Adjustments in antibiotic dosage may be required for anuric patients sustained on peritoneal dialysis or hemodialysis. Information is incomplete for many antibiotics, and *the following schedule is only an approximate guide*. Drugs not mentioned below should not be used since information on them is not available, and safer antibiotics can be used.

a. Dosage as in anuria (see Table 2):

(1) Excreted or inactivated by non-renal mechanisms:

erythromycin
chloramphenicol
(?ampicillin*)

(2) Not removed by dialysis:

polymyxin
colistin
vancomycin
lincomycin
oxacillin
cloxacillin
methicillin

*Information inadequate.

(?penicillin*)
(?dicloxacillin*)

b. *Minor dosage adjustment required* — for drugs which are partially removed by dialysis:

(1) *Hemodialysis*—dosage schedules are relatively well established for patients on chronic twice-weekly dialysis:

tetracycline

(oral) — 0.5 Gm post-dialysis

streptomycin — 0.5 Gm post-dialysis

gentamicin — 1 mg/kg post-dialysis

kanamycin — 7.5 mg/kg post-dialysis

INH — } 300 mg post-dialysis
 — } then
 — } 100 mg + pyridoxine q 24 h

(2) *Peritoneal dialysis* — Since long-term regular peritoneal dialysis is rarely used, guidelines for antibiotic dosage are less clearly established. Insufficient amounts of tetracycline are removed to be of significance, and the dosage recommended for the anuric patient should be used. More substantial amounts of kanamycin and streptomycin (and possibly gentamicin) are removed; the dosage suggested for patients on hemodialysis could be used, but the appropriateness of this is uncertain.

c. *Dosage adjustment probably required*—information not adequate:

amphotericin

cephalothin

cephaloridine

It should also be noted that dialysis (peritoneal or hemodialysis) should be used in the management of overdosage with kanamycin and possibly streptomycin and gentamicin, but is unlikely to be of value with other nephrotoxic antibiotic intoxications.

Antibiotics should not be added to the dialysing fluid used in peritoneal dialysis, since they are of no value as prophylaxis against infection and may get absorbed and accumulate in the body.

Table 2 provides an approximate guide to dosage for antibacterial agents in patients with renal insufficiency. Much of the information currently available is inadequate, and this guide cannot be regarded as definitive. It should be appreciated that in any individual patient such a dosage guide could result in inadequate or hazardous drug levels unless clinical and laboratory guides are obtained concurrently and appropriate dosage adjustments made as necessary.

* Information inadequate.

ANTIBIOTICS AND LIVER DISEASE

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The following outline is an attempted compilation of known information to serve as a guide in using antibiotic therapy in patients with (a) underlying liver disease and (b) acute liver and gallbladder infections. Unfortunately, precise information is inadequate for many of the drugs. For some drugs very little human data is available for liver tissue antibiotic concentrations, liver histology during treatment, bile levels, and precise metabolic processes in the liver. Indeed, for many older drugs and drugs that are little used, even animal data is scanty.

It is emphasized that often animal data is not applicable to man. A good example is isoniazid, which given long term to dogs produces fatty changes and jaundice; this development is rare in man.

For the most part in treating patients with pre-existing liver disease who develop infections outside the liver, one should use caution in prescribing drugs known to be dependent on liver for inactivation or excretion. Usually a safer substitute drug can be found. If a potentially toxic drug must be used, blood levels can be useful in monitoring the dose to within safe limits. One should also take care to avoid use of hepatotoxic non-antibiotic drugs concomitantly.

On the other hand, drugs metabolized and/or excreted by the liver are theoretically ideal for treatment of acute infections of liver and biliary tract.

I. Penicillin G

1. Metabolism by liver: Only minor fraction is ordinarily handled by liver, but in impaired renal function the liver may be a major excretion route via bile.

2. Liver tissue levels: Significant

3. Bile levels: Significant concentration

4. Liver toxicity: Rarely, as part of a generalized hypersensitivity reaction

5. Dose in liver disease:

(a) No change if renal function is good

(b) Reduce dose in circumstance of combined kidney and liver disease.

6. Comment: All penicillins are concentrated in bile even if absolute amount of hepatic excretion is small.

II. Alpha-phenoxy-penicillins

- A. Phenoxymethyl
- B. Phenoxyethyl (phenethicillin)
- C. Phenoxybenzyl (phenbenicillin)

Generally the information for penicillin G applies also for this group. One unique feature of phenbenicillin is that 20% of a dose appears in urine in the form of two metabolites, rather than in unchanged form as with the other penicillins. Site of the metabolic conversion is unknown.

III. Beta Lactamase-Resistant Penicillins

A. Methicillin. Generally the information for penicillin G applies to methicillin.

- B. Oxacillin
- C. Cloxacillin
- D. Nafcillin

Oxacillin and nafcillin have a high percentage excretion into bile. Indeed, with nafcillin, up to 90% of an I.V. dose is accounted for in bile. Oxacillin has induced mild reversible SGOT rises, in one case with a palpable liver.

IV. Broad-Spectrum Penicillins

- A. Ampicillin
- B. Hetacillin
- C. Carbenicillin

Generally the information for penicillin G applies to this group. Ampicillin concentrations in bile may reach as high as 300 times that concurrently present in the plasma; however, the kidneys still account for the major function of the excretion, perhaps 80 percent or more.

In two reports, up to 30 percent of patients on hetacillin 1-2 Gm/day P.O. or I.M. developed laboratory liver function abnormalities without clinical signs; these usually reverted after stopping drug.

I.M. injection of ampicillin in doses of 1 Gm or more can be associated with modest SGOT elevations, which return to normal after stopping drug. The SGOT is possibly released from muscle, rather than liver.

V. Cephalosporins

- A. Cephalothin

1. Metabolism by liver: 70-80% usually excreted unchanged in urine. However, it can be inactivated by deacetylation (presumably in liver), then excreted in urine.

2. Liver tissue levels: No information on humans; not concentrated in rats' livers.

3. Bile levels: No good data available.

4. Liver toxicity: Occasional SGOT rise

5. Dose in liver disease: Advisable to decrease in presence of combined renal-hepatic disease.

6. Comment: Many patients develop a positive Coombs' test on drug, but this doesn't correlate with a hemolytic state.

B. Cephaloridine

1. Metabolism by liver: No data; but 70-75% of the drug is accounted for in unchanged form in urine. (There is no acetyl group to split off this compound, as there is with cephalothin.)

2. Liver tissue levels: In rabbits on 200 mg/kg simultaneous levels are:

	LIVER (mcg)	SERUM (mcg)
@ ½ hr.	30	100
@ 4 hr.	25	10

In a patient on 1 Gm q4h who died, assay of serum and liver tissue respectively were 58 mcg/ml and 31 mcg/ml.

3. Bile levels: Equal to or below serum.

4. Liver toxicity: Drug may regularly cause modest rise in SGOT, which often reverts while drug is continued. May regularly cause prolonged prothrombin time (up to 29 sec.), though no hemorrhage reported.

5. Dose in liver disease: Same as for cephalothin.

VI. Streptomycin and Dihydrostreptomycin

1. Metabolism by liver: Small fraction is secreted into bile.

2. Liver tissue levels: Appreciable.

3. Bile levels: Not concentrated; up to 10-20 mcg/ml on high doses.

4. Liver toxicity: Rarely reported; also rarely may aggravate existing liver disease.

5. Dose in liver disease: No change.

VII. Tetracyclines

Chlortetracycline, oxytetracycline, tetracycline, demethylchlortetracycline, methacycline, doxycycline

1. Metabolism by liver: All tetracyclines are concentrated in liver and excreted via bile into intestine, where they are reabsorbed. Variable amounts of each member of this drug family are

thereafter eliminated in urine. Chlortetracycline has only 18% eventually eliminated by urine, whereas tetracycline has 60%, oxytetracycline 70%, and methacycline and demethylchlortetracycline 60-70% eliminated eventually in urine. Methacycline and demethylchlortetracycline have prolonged half-lives in the serum because of slower ($\frac{1}{2}$) renal clearance than that of tetracycline or oxytetracycline.

2. Liver tissue levels: All are concentrated.

3. Bile levels: 5-32 x the serum level.

4. Liver toxicity: With excess parenteral dose, patients get abnormal LFT's progressing to acidosis, shock, coma and death. Liver lesion is fatty vacuolization with little or no necrosis or biliary stasis. Other organs which may suffer simultaneous toxicity are pancreas, kidneys and brain. Pregnancy and chronic renal disease seem to predispose patients to this type of hepatotoxicity.

5. Dose in liver diseases: Some studies show $\frac{1}{2}$ - $\frac{2}{3}$ of patients with pre-existing hepatic disease get increased fat in liver cells while on tetracyclines. This may revert after stopping drug.

Recommend 1 Gm/day as maximum parenteral dose or use different drug in pregnancy, advanced liver disease, renal disease, or combined hepatic-renal disease. Avoid chlortetracycline completely in liver disease. If dosage adjustment is necessary, avoid exceeding a blood level of 10 mcg/ml.

6. Comments:

(a) By fluorescence and autoradiography, it is demonstrated that liver and kidney concentrate tetracyclines (in mitochondria) more than other organs. Tetracyclines have adverse effects on several hepatic enzymes.

(b) Inactivated chlortetracycline causes same toxic hepatic changes as the active drug; so hepatic toxicity appears not related to antibacterial activity (in mice, dogs).

(c) Tetracyclines may reduce blood coagulation by altering physicochemical characteristics of blood lipoproteins.

(d) Via probable changes in intestinal flora, tetracyclines may decrease plasma prothrombin, and increase urine bilirubin while decreasing urine urobilinogen. This ordinarily causes no clinical problem.

VIII. Chloramphenicol

1. Metabolism by liver: 85-95% is conjugated in liver to monoglucuronide; 3% is further converted to aryl amines and aryl nitro derivatives. Most of above is secreted then by kidney tubules.

2. Liver tissue levels: Concentrated.

3. Bile levels: Average $\frac{1}{2}$ that of plasma.

4. Liver toxicity: Rare.

5. Dose in liver disease: Use caution. If ascites or jaundice is present, use under 25 mg/kg/day or another drug.

6. Comments:

(a) Bone marrow toxicity correlates with high serum levels of free drug; there is no known correlation with levels of metabolic products. It is desirable to keep serum level below 25 mcg/ml of free drug. Though overall chloramphenicol metabolism isn't greatly reduced in hepatic insufficiency, conjugation is slowed and allows more vulnerability to bone marrow toxicity.

(b) Newborns are vulnerable to "grey syndrome" due to immature hepatic and renal function.

IX. Macrolides

A. Erythromycin

1. Metabolism by liver: Major excretory pathway; it is excreted into bile in active form.

2. Liver tissue levels: Concentrated.

3. Bile levels: Concentrated to 5x plasma levels. The estolate form is excreted less in bile than other forms.

4. Liver toxicity: Only by estolate form. Up to 16% of patients after 10-14 days' therapy or repeated courses get elevated transaminase; up to 4% get jaundice with hepatitis symptoms and cholestatic hepatitis on biopsy.

5. Dose in liver disease: Avoid estolate form. Other forms in usual dosage.

6. Comments: Estolate-induced hepatitis is a hypersensitivity reaction. Look for eosinophilia. The syndrome may be reactivated later with a small single oral re-challenge dose of drug.

B. Oleandomycin and triacetyloleandomycin

1. Metabolism by liver: Major.

2. Liver tissue levels: No good data available.

3. Bile levels: Up to 10-15x the peak serum level.

4. Liver toxicity: None from oleandomycin. On triacetyloleandomycin 1 Gm qd x 14 days, up to over 50% of patients may get abnormal liver function tests with or without clinical symptoms. Changes may be dose dependent. Liver biopsies show mixed changes with hepatocellular damage, cholestasis, periportal infiltration and eosinophilia.

5. Dose in liver disease: Avoid.

X. Lincomycin

1. Metabolism by liver: Major; it is excreted and re-excreted via enterohepatic circulation.

2. Liver tissue levels: No data.

3. Bile level: High; can be 10-20x the serum level.

4. Liver toxicity: Occasional jaundice and/or abnormal liver function tests which clear rapidly, sometimes even while drug is continued. No histological information available.

5. Dose in liver disease: Half-life of drug is doubled. Accordingly drug dose should be reduced, or drug avoided entirely.

6. Comment: Relatively new drug, and experience incomplete.

XI. Novobiocin

1. Metabolism by liver: Major.

2. Liver tissue levels: No good data available.

3. Bile levels: 1½-8x serum level.

4. Liver toxicity: uncommonly, liver cell necrosis; occasional patients get biochemical lesion.

5. Dose in liver disease: Unknown, but probably is best to avoid.

6. Comments: This drug may induce "jaundice" by five different methods, all generally uncommon:

(a) Inhibition of glucuronyl transferase in newborns. Up to 7% get high indirect bilirubin and danger of kernicterus without associated liver cell morphological damage.

(b) After 2-14 days' therapy, 0.6% of patients get yellow discoloration of plasma, skin, and sclerae; this is controversially held to be secondary to a circulating lipochrome pigment degradation product of novobiocin.

(c) Occasional adults get increased uncon-

jugated bilirubin and BSP retention with no evidence of morphological disease.

(d) Occasional hemolytic anemia.

(e) Occasional hepatocellular morphological damage with or without cholestasis.

XII. Kanamycin-Neomycin-Paromomycin Group

A. Kanamycin

1. Metabolism by liver: Nil.

2. Liver tissue levels: No data.

3. Bile levels: Up to 10-20x serum levels (but absolute amount is less than 0.5% of total amount of a 1 Gm test dose).

4. Liver toxicity: No.

5. Dose in liver disease:

(a) No change in parenteral dose.

(b) For oral form, see comments.

6. Comments:

In severe liver disease, oral kanamycin at 8 Gm/day eventually builds serum levels to therapeutic range. This effect is even greater with hepatic disease and azotemia. Accordingly, such patients on gut sterilization with kanamycin should be watched for deafness and increasing nephropathy.

B. Neomycin

1. Metabolism by liver: No.

2. Liver tissue levels: No data.

3. Bile levels: No good data available.

4. Liver toxicity: No.

5. Dose in liver disease: No more than 6 Gm P.O. for gut sterilization. If azotemia also present, kanamycin is preferred.

6. Comments: Same apply as for kanamycin. Notably with hepatic disease and azotemia, blood levels on 4 Gm/day P.O. may eventually reach those achieved on parenteral therapy in normals.

C. Paromomycin

This drug is only used orally for gut sterilization, and is only minimally absorbed. There is no liver toxicity. Probably kanamycin is preferred for gut sterilization in hepatic coma with azotemia.

XIII. Polymyxin - Colistin Group

1. Metabolism by liver: Minor, if any.

2. Liver tissue levels: No good data available.

3. Bile levels: Low.
4. Liver toxicity: No.
5. Dose in liver disease: No change.

XIV. Vancomycin

This drug is minimally, if at all, metabolized by liver. Very little is present in bile. No liver toxicity is reported.

XV. Nitrofurantoin

1. Metabolism by liver: 50-60% is metabolized at unknown site.
2. Liver tissue levels: No good data available.
3. Bile levels: No good data available.
4. Liver toxicity: Rarely, causes a hypersensitivity hepatitis with cholestasis, focal necrosis, infiltrates, eosinophils.
5. Dose in liver disease: Probably no change.
6. Comment: May cause hemolytic anemia with jaundice in G6PD deficient patients.

XVI. Sulfonamides

1. Metabolism by liver: Metabolism is significantly, but not solely by liver (acetylation, glucuronidation, and/or oxidation), then excreted into urine.
2. Liver tissue levels: Significant.
3. Bile levels: Similar to plasma.
4. Liver toxicity: Two types, not influenced by dose: direct hepatotoxicity and hypersensitivity. Either may go on to acute yellow atrophy.
5. Dose in liver disease: Best to avoid sulfas.
 - (a) Pre-existing nutritional liver disease may predispose to sulfonamide hepatotoxicity.
 - (b) Kidneys appear to be more susceptible to damage by sulfas in patients with chronic liver disease.
 - (c) Neonates have reduced acetylation, thus require less dose for therapeutic blood levels.
6. Comments:
 - (a) Incidence of reported hepatic injury secondary to sulfonamides is greatly decreased (to 0.1%) since the introduction of sulfadiazine and subsequent other new compounds.
 - (b) Acetylated and glucuronide forms circulating in blood prior to renal excretion contribute to toxicity but not to antibacterial effect.
 - (c) Sulfas may induce hemolytic anemias in G6PD deficient patients.

- (d) Long-acting forms are particularly dangerous in the event of a toxic reaction since drug levels persist long after the drug is discontinued.

XVII. Amphotericin B

1. Metabolism by liver: Minor.
2. Liver tissue levels: No good data available.
3. Bile levels: No good data available.
4. Liver toxicity: May be rarely idiosyncratic, or due to excess dose (i.e., greater than 1 mg/kg/dose). The picture is acute failure with toxic degeneration, fatty liver and cholestasis.
5. Dose in liver disease: Unknown, but caution advised.

XVIII. Antituberculosis Drugs

A. Streptomycin: See above.

B. Isoniazid.

1. Metabolism by liver: 40-90% is excreted by kidneys; but a significant variable amount is inactivated by acetylation and other changes via liver enzyme(s), then excreted in urine.
2. Liver tissue levels: High.
3. Bile levels: Data in rabbits suggest $1\frac{1}{2}$ x the average serum level.
4. Liver toxicity: Rarely on therapeutic doses, patients may get either toxic or hypersensitivity hepatitis.
5. Dose in liver disease: Probably no change.
6. Comments: About 50% of patients are "slow inactivators," an autosomal homozygous recessive trait, i.e., they acetylate INH slowly, thereby having prolonged active drug levels. Slow inactivators should take pyridoxine daily. Some workers feel "rapid inactivators" should get maximum doses for T.B. meningitis, but standard doses for pulmonary T.B. are adequate.

Note: Pyridoxine is a coenzyme of transaminases, and given daily may cause spuriously elevated transaminase activity.

C. Para-aminosalicylic acid

1. Metabolism by liver: 50-65% is acetylated (possibly by a liver enzyme), then excreted into urine.
2. Liver tissue levels: High.
3. Bile levels: No good data available.
4. Liver toxicity:
 - (a) Generalized hypersensitivity reactions (2-5%) may progress to include liver cell

necrosis (uncommon), and/or cholestasis; it may be fatal.

(b) May suppress prothrombin formation in liver; usually not a clinical problem.

5. Dose in liver disease: No good data available.

6. Comments:

(a) Continued use of drug in presence of early hypersensitivity reactions can lead to progression to more serious symptoms. Accordingly, drug should be discontinued. Some workers feel desensitization can be done successfully.

(b) Occasional hemolytic anemia occurs.

(c) Apparently competes with INH for acetylation, thereby increasing free INH levels.

D. Ethionamide

1. Metabolism by liver: Unknown, but less than 1% is excreted in urine in active form.

2. Liver tissue levels: Same as blood presumably.

3. Bile levels: Data in rabbits suggest $1\frac{1}{2}x$ average serum level.

4. Liver toxicity: Occasional toxic or hypersensitivity hepatitis, usually in diabetics.

5. Dose in liver disease: Unknown; close monitoring of renal and hepatic function advised.

E. Pyrazinamide

1. Metabolism by liver: Minor.

2. Liver tissue levels: No good data available.

3. Bile levels: No good data available.

4. Liver toxicity: Toxic hepatitis in 10-20% of patients is dose dependent and usually occurs late (2nd-6th month). It may be fatal.

5. Dose in liver disease: Avoid.

6. Need for careful monitoring of liver functions limits its usefulness.

F. Cycloserine

1. Metabolism by liver: 35% is metabolized at unknown site(s).

2. Liver tissue levels: No good data available.

3. Bile levels: Present, but none reaches stool.

4. Liver toxicity: Not reported.

G. Ethambutol

1. Metabolism by liver: 70-95% is excreted in urine of which 8-15% appears as metabolites. Site of the conversions is unknown.

2. Liver tissue levels: No good data available.

3. Bile levels: Unknown.

4. Liver toxicity: Mild SGOT rise noted in some patients on 25 mg/kg for several months.

5. Dose in liver disease: No change.

6. Comment: New dose recommendation is 15 mg/kg/day in patients on drug over 60 days. This gives adequate therapeutic effect, and avoids ocular toxicity and SGOT elevations.

H. Viomycin

Metabolism by liver is minimal. Very little is known of its metabolism except it is mainly excreted in urine. No liver toxicity reported.

MEDICAL STAFF CONFERENCE

Eosinophilia and Eosinophilic Carditis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* The discussion today relates to eosinophilia. The case presentation will be given by Dr. Homer Boushey.

DR. BOUSHEY:† This 48-year-old Caucasian male was a disabled laborer who was admitted to the hospital for the fifth time on 1 July 1969 for severe chest pain and recurrent shortness of breath. In 1965 tenderness and swelling of the right calf developed and thrombophlebitis was diagnosed. At that time an eosinophil count of 10 percent was noted. The disease appeared to respond to symptomatic therapy; however, after leaving the hospital the patient continued to have painful swelling of both calves and noted weight loss and wasting of the muscles of the legs. Consequently, he reentered the hospital. A muscle biopsy was interpreted as showing acute eosinophilic myositis at a time when the peripheral eosinophil count was 21 percent. The patient first noted palpitations during that stay in hospital.

In 1968 the patient entered this hospital for the first time. Serum levels of "muscle enzymes" were elevated. The diagnosis of eosinophilic myositis was confirmed by a muscle biopsy in which nearly all the inflammatory cells seen were eosinophils.

Screening tests, including upper gastrointestinal series, barium enema, and sigmoidoscopy, were negative. A gastric ulcer was found which subsequently responded to medical management. Cardiomyopathy was also diagnosed on the basis of

cardiomegaly, conduction defects, and arrhythmias, including wandering atrial pacemaker and intermittent two to one A-V dissociation.

In September 1968 the patient was admitted to the neurology service for evaluation. On the day of entry he had a syncopal episode and was found to have complete heart block. A pacemaker was inserted which produced good control of the ventricular rate. At that time peripheral eosinophils were only 1.0 percent with an absolute count of only 74 per cu mm. Corticosteroid therapy was started but discontinued because of exacerbation of abdominal pain associated with a recurrent gastric ulcer.

The patient entered this hospital for the third time in December 1968 because of incomplete small bowel obstruction, which responded to conservative management. During this period the patient's congestive heart failure increased in severity, probably as a result of fluid overload. The patient left the hospital and did relatively well with no specific medication for the myositis. He gained weight and generally felt better.

In April 1969 he entered this hospital for the fourth time, because of recurrent shortness of breath. Intermittent failure of the pacemaker to capture the ventricle was noted, and a pacemaker was reinserted with good control of the ventricular response. He continued, however, to have episodic shortness of breath, increasing cardiomegaly, and pleural effusions. A lung scan showed multiple perfusion defects consistent with pulmonary emboli, and anticoagulant therapy was given. Eosin-

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†Homer Boushey, M. D., Resident in Medicine.



Figure 1.—Radiographic film taken in April 1968, showing normal heart size.



Figure 2.—Radiographic film taken in April 1969, showing increased heart size.

ophils during this admission were never higher than 0.5 percent and an absolute count was 143 per cu mm.

The patient last entered this hospital on 1 July 1969 for evaluation of severe pain of eight hours' duration occurring two days before admission. This pain radiated from the left side of the chest to the right. He had increasingly severe shortness of breath but no cough or hemoptysis.

On physical examination the patient appeared wasted and chronically ill with sunken cheeks and eyes. A livido reticularis pattern was present over the trunk and extremities; the ear lobes were cyanotic. The jugular venous pulse was elevated to 4.0 cm above the clavicles at 30° elevation. The point of maximal impulse was diffusely located over the fifth intercostal space, 1.0 to 2.0 cm lateral to the midclavicular line. A grade ii/vi systolic ejection murmur and a prominent S_3 gallop were heard but no S_4 was evident. The liver was not palpable and there was no peripheral edema. Pronounced generalized muscle wasting was present with no differential between the proximal and distal muscle groups. Results of neurological examination were within normal limits.

An electrocardiogram showed no important change from previous tracings. Leukocytes numbered 7,000 per cu mm of blood, with no eosinophils. The serum glutamic oxalic transaminase and creatine phosphokinase were elevated as they had been on all previous admissions, presumably

because of muscle disease. A lung scan showed considerable clearing since the last admission and no new perfusion defects.

On 3 July 1969 cyanosis and hypotension developed, and a harsh pericardial rub was heard over the entire precordium. Prednisone therapy was begun for the possibility of eosinophilic myositis and pericarditis, but shortly afterward the patient died.

DR AMBERG:* Here is a series of x-ray films beginning 11 April 1968 when the cardiomyopathy was first diagnosed. It is evident that the heart size was completely normal at that time (Figure 1). When he entered the hospital with complete heart block, the heart size was very slightly enlarged. A pacemaker was inserted, and the heart size returned to normal. In April 1969, one year later, the pacemaker failed and the heart size again increased considerably; the patient was in frank congestive failure with much pulmonary congestion (Figure 2). The decubitus film showed free pleural effusion.

DR. SMITH: I suppose now it is unnecessary to introduce Dr. Amberg. We are delighted to have him here representing the Department of Radiology. He is Professor of Radiology and was formerly Chief of the Radiology Department at Fort Miley Veterans Administration Hospital in San Francisco.

*John R. Amberg, M.D., Professor of Radiology.

TABLE 1.—*Conditions Associated with Eosinophilia*

Drug Reactions	
Examples:	Iodide Penicillin
Parasitosis	
Examples:	Trichinosis Visceral larva migrans
Infections	
Leprosy	Fungal
Brucellosis	infections
Tuberculosis	Scarlet fever
Malignancies	
Carcinoma:	Lung Ovary Stomach
Hodgkin's disease	
Collagen Disease	
Periarteritis nodosa	
"Cutaneous"	
Pemphigus	
Dermatitis herpetiformis	
Loeffler's Syndrome	
Farmer's Lung	
Asthma, Hay Fever	
Leukemia	
Chronic myelocytic	
Eosinophilic	
Eosinophilic Endocarditis	(Loeffler's Endocarditis)
?Radiation	
Unknown Cause	
Idiopathic	Cigarette smoking
Sarcoidosis	Tropical eosinophilia

This patient had a very complex illness extending over a four-year period and leading to death with cardiac complications. We have asked Dr. Martin Cline to discuss the patient and the disease entity which this patient represents. We have asked him to focus more specifically on the significance of the eosinophil, its normal function, and the disorders which call forth high levels of this peculiar cell.

DR. CLINE: * Dr. Smith, it is a privilege to be here; it is always flattering when a hematologist is asked to discuss that organ involved in the propulsion of blood rather than the fluid and cellular elements. I shall, however, resist the temptations to discuss the nuances of electrocardiographic abnormalities in eosinophilic carditis. Instead I would like to examine an approach to the diagnostic problem of eosinophilia and to consider where the clinical picture presented this morning may fit into such a classification. Finally I should like to consider the eosinophil itself and its possible pathogenetic significance.

* Martin J. Cline, M.D., Associate Professor of Medicine and Radiology and Associate Director, Cancer Research Institute.

The list of diseases associated with eosinophilia can be gleaned from any standard textbook of medicine and several weeks in the library (Table 1). It is a list familiar to most of you. With your indulgence, I will briefly examine this catalogue in order to place our patient in proper perspective.

Perhaps the commonest form of eosinophilia seen in our hospital at present is that related to drug reactions. Of these probably the most common is sensitivity to antibiotics; although any of a number of drugs may be associated with eosinophilia.¹ The next most common cause of significant eosinophilia seen on our medical service is parasitic infections. The nematodes are the parasites *par excellence* associated with eosinophilia. As a generalization, tissue phases of parasites are much more apt to provoke significant levels of blood eosinophilia than is parasitization of the gut alone.

Visceral larva migrans, as part of the "cat sandbox syndrome," is one of the more interesting causes of parasitic eosinophilia and deserves some comment.² This condition is occasionally diagnosed as eosinophilic leukemia. I can clearly remember a small child entering the National Institutes of Health with pronounced hepatosplenomegaly, a blood eosinophil count in the range of 100,000 per cu mm, and a diagnosis of eosinophilic leukemia. Because of the extreme rarity of true eosinophilic leukemia, other diagnostic possibilities were pursued. A liver biopsy demonstrated the typical histologic features of *Toxocara canis*.

Eosinophilia may also be part of a number of infectious processes, including tuberculosis, brucellosis, fungal infections, leprosy, and scarlet fever. It is quite interesting to me to observe some of the names associated with the descriptions of eosinophilia and infection. Franz Ingelfinger,³ the prominent gastroenterologist and now Editor of the *New England Journal of Medicine*, was one of the first to call attention to the presence of eosinophilia in brucellosis.

Because increase in the number of blood eosinophils is sometimes associated with malignant lesions, an intensive search for the presence of occult neoplasms was made in the patient whose history was presented today. By far the most common malignant change in which eosinophilia is a prominent feature is Hodgkin's disease. In this disorder eosinophil concentrations may reach the level of 50,000 to 70,000 per cu mm. Occasionally eosinophilia is reported in association with car-

cinoma of the stomach, lung and ovary. From my own experience, I can recall one patient with carcinoma of the lung and eosinophils in the range of 50,000 per cu mm.

Among the connective tissue diseases, periarteritis nodosa has been most frequently associated with eosinophilia. It is reported that eosinophilia is rare in periarteritis in the absence of pulmonary involvement; with pulmonary involvement, it is quite common. Rheumatoid arthritis may also occasionally be associated with significant blood eosinophilia.

The concurrency of certain cutaneous diseases and elevated levels of blood eosinophils is well known, although the mechanism involved is, of course, quite obscure.

Loeffler's syndrome consists of blood eosinophilia, transient pulmonary infiltrates, and eosinophils appearing in the sputum.⁴ Usually the pulmonary infiltrate persists no longer than two weeks; Loeffler himself used the word *fluchtig*, meaning fleeting. The course is generally benign and the cause unclear, although it has been suggested that in some patients the clinical manifestations are the result of the migration of certain parasites through the lungs as part of their life cycle.

Farmer's lung as a cause of eosinophilia is thought to result from the inhalation of mold and a subsequent allergic reaction. The eosinophil may be one of the prominent cells in the acute inflammatory process in this condition.

Association of eosinophilia with asthma and hay fever is, of course, well known. There are some interesting sub-syndromes within these disease categories. At the University of California hospitals two patients were seen recently who had abrupt onset of asthma, fleeting pulmonary infiltrates in an unusual distribution, and a high blood concentration of eosinophils. Both the asthma and the eosinophilia responded dramatically to treatment with adrenocorticosteroids. These patients may have had a recently described disease syndrome, chronic eosinophilic pneumonia.⁵ In one of the references which I have given you,⁶ there is a notation that patients dying in acute asthmatic attacks may have eosinophilic infiltration of the myocardium as well as patchy myocardial fibrosis. This may have some bearing on what I am going to discuss shortly.

Eosinophilia may be a part of the disease picture of chronic myelocytic leukemia, just as increased blood basophilia is a frequent finding. Eosinophils

are rarely the predominant cell in this disorder, but the absolute number of these cells is often increased. I am going to spend most of the next few minutes talking about two diseases: eosinophilic leukemia and eosinophilic endocarditis. The patient presented today may have had eosinophilic carditis. For the sake of completeness, however, I should like to finish my cataloging and then return to these entities.

Exposure to irradiation is said to be associated occasionally with elevated levels of blood eosinophils. One tends to dismiss this association because one cannot readily conceive of the mechanism; however, in my own limited experience I have seen two patients with history of significant exposure to irradiation who had prominent blood eosinophilia. One patient was a technician at the Livermore Laboratories and the clinical manifestations resembled those of eosinophilic leukemia over a course lasting several years.

In Table 1 I have included a category of eosinophilia of unknown cause (not suggesting, however, that we know the cause of the eosinophilia in those diseases already cited). Tropical eosinophilia is a disease characterized by blood eosinophilia and nocturnal cough; it was a significant problem among combat personnel in the Korean War. The cause may be microfilarial parasitization.⁷

Within the category of eosinophilia of unknown origin, there is at least one recorded case of eosinophilia occurring in a patient whenever he smoked cigarettes.⁸ Eosinophilia may also occur in sarcoidosis. I found an interesting reference to eosinophilia and "chronic nervous exhaustion" in the *American Journal of Insanity*. Unfortunately that journal stopped publication in the early 1920s, and I was unable to get an adequate follow-up and documentation of this particular cause.

Finally, there is an entity called "idiopathic eosinophilia" which does not conveniently fit into any of the previously mentioned disease categories. The important point to remember is that idiopathic eosinophilia is generally a benign condition. In a good study⁹ in which 38 patients with idiopathic eosinophilia were followed, six died during a five-year period—two of chronic myelocytic leukemia, one of carcinoma of the stomach, and the other three of apparently unrelated causes. In general, therefore, idiopathic eosinophilia appears to be without serious pathologic import.

I would like to consider briefly eosinophilic leukemia and whether or not it exists as a disease

entity. Until 1960 there were approximately 30 cases of so-called eosinophilic leukemia in the world's literature. This "leukemia" had certain rather peculiar features¹⁰: In the reported cases anemia as well as thrombocytopenia were somewhat rare. In addition, an extremely high incidence of myocardial involvement was reported, and most of the patients died either of myocardial failure or of peripheral embolization. I believe that most of these descriptions of "eosinophilic leukemia" are actually examples of the syndrome of *eosinophilic endocarditis*. It is likely, however, that eosinophilic leukemia does exist as a separate disease entity; it is, however, extremely rare and considerably less common than eosinophilic carditis. The statement that eosinophilic leukemia does exist is based on the occurrence of the Philadelphia chromosome in a patient with blood eosinophilia, organomegaly, and diffuse organ infiltration with eosinophils.¹¹ This patient subsequently died in a blast crisis. The entire clinical and pathological picture was quite compatible with that of chronic granulocytic leukemias.

The patient presented this morning was thought to have "fibroplastic parietal endocarditis with blood eosinophils," a disease process described by Loeffler in 1936 in the *Swiss Journal of Medicine*.¹² The major clinical features of the original case were significant: peripheral blood eosinophilia, cardiac failure, and peripheral emboli. At autopsy the patient was found to have fibrosis involving the walls of the heart rather than the valves. Both the ventricular walls and the septum were fibrous, and mural thrombi were present. Since the original report of this entity, there have been approximately 40 cases described. Eosinophilic endocarditis is the usual name applied to the syndrome.

The clinical characteristics of these 40 cases are briefly summarized in Table 2. Although a wide age range has been represented, most cases have been in adults, usually between 30 and 50 years of age and predominantly in males. Almost all the initial reports were from Europe and thus involved a Caucasian population. More recently there have been several cases reported from South Africa involving Negroes.¹³ The onset of symptomatic disease has varied from acute to gradual. The duration of disease has also ranged widely from three months to six years; however, I would point out that almost half of the patients died within a year of the onset of significant symptoms. It is a highly

TABLE 2.—*Eosinophilic Carditis: Clinical Features in Approximately 40 Patients*

Age Range
7 to 65 years
(Usually 30 to 50 years)
Male to Female Ratio
3:1
Population
Negro and Caucasian
Onset
Acute or gradual
Duration
3 months to 6 years
(19 out of 40 patients died within 12 months)
Manifestations
Afebrile
Eosinophilia
Electrocardiogram
Nonspecific ST and T changes
(16 out of 40 patients)
Left ventricular hypertrophy
(3 out of 40 patients)
Possible embolic phenomenon
Murmur of mitral insufficiency
(20 out of 40 patients)
Possible central nervous system signs
Therapy
Poor response

lethal disease. Additional manifestations have included central nervous system signs, with seizures being the most prominent feature. Peripheral and pulmonary embolic phenomena have been common. Approximately half of the patients described had a murmur consistent with mitral insufficiency; in the other half the murmur was not clearly defined. There was often a disparity between heart size and the degree of congestive failure, a phenomenon characteristic of constrictive pericarditis. I visualize this disparity as resulting from extensive fibrosis of the endocardium. The course was in general afebrile. Most of the patients had persistent eosinophilia ranging from 30 to 70 percent, but a few were reported as having only very transient blood eosinophilia even though there was eosinophilic infiltrate in organs, including the heart. Electrocardiograms were generally not helpful because they lacked specificity. Only three patients had electrocardiographic evidence consistent with left ventricular hypertrophy. A characteristic feature of the disease entity was a poor response to therapy, including cardiac glycosides and other routine methods of treating congestive heart failure.

Eosinophilic endocarditis has a rather characteristic pathologic picture (Table 3): Early in the disease there is evidence of endocardial and myocardial necrosis distributed in a spotty fashion throughout the heart. These early lesions may be

TABLE 3.—*Pathologic Features of Eosinophilic Carditis*

Early Features
Necrosis
Endocardial
Myocardial
Possible small vessel inflammation
Cellular infiltrate with eosinophils
Late Features
Fibroelastosis
Chronic inflammatory changes

accompanied by inflammation of small vessels, and eosinophils are the predominant cellular infiltrate. Near the time of death there are generally extensive fibrotic changes in which both collagen and elastic tissue are involved. In these chronic inflammatory lesions eosinophils may persist, but in general the predominant cell types are macrophages and lymphocytes.

Taken together, the major clinical and pathologic features of the syndrome are

- Refractory congestive heart failure
- Blood eosinophilia
- Endocardial and myocardial fibrosis (usually involving the right ventricle more than the left)
- Frequent mural thrombi and peripheral emboli.

Did the patient presented this morning in fact have eosinophilic endocarditis? The clinical phenomena were consistent with this disease except that eosinophilia was only transient. Among the reported cases, fleeting eosinophilia is extremely rare. The following is a review of the pathologic findings at autopsy: The major pathologic change was limited to the heart which grossly showed endocardial fibrosis primarily involving the right ventricle. Microscopy revealed scattered myocardial fibrosis. In most areas the fibrosis was of long standing, and chronic inflammatory cells rather than eosinophils were present. There were a few areas that appeared to be of recent origin in which eosinophilic infiltrates were present.

I think the patient whose case we are considering today had an unusual variant of eosinophilic endocarditis in that he did not die during a phase of acute blood eosinophilia or of eosinophilic infiltration of the tissues.

I would now like to discuss the eosinophil itself; perhaps what we know of this cell will help to explain some of the pathologic changes or pathogenetic mechanisms of eosinophilic carditis. This is the basic question: Is the eosinophil pathogenic in this disease entity or is it merely an accompani-

TABLE 4.—*Characteristics of Eosinophils*

Motile
Granules
Poor in lysozyme
Rich in peroxidase
Contain protein inclusions
Phagocytic of Microorganisms
(Less phagocytic than neutrophils)
Phagocytic of Antigen-Antibody Aggregates
Attraction by Antigen-Antibody Aggregates

ment of other primary pathologic processes—an epiphenomenon, as it were?

When discussing a similar case two years ago there was only one thing I was very secure about: Eosinophils are red. Since that time we have gained some additional knowledge (Table 4). Eosinophils have crystalline inclusions within their granules. The inclusions are protein, but the nature of the protein is unknown. The granules are poor in lysozymes (presumably they are not involved in the degradation of certain bacterial cell walls) but have a great deal of peroxidase.¹⁴ This peroxidase is chemically and immunologically distinct from the myeloperoxidase of the neutrophil. Human eosinophils are probably rich in antibacterial, cationic proteins, although this fact has not been clearly substantiated. Like granulocytes, eosinophils are motile and phagocytic of microorganisms. They are not, however, either as motile or as phagocytic as the neutrophils.¹⁵

Two characteristics of the eosinophil which have generated the most attention and speculation are their attraction by antigen-antibody aggregates and their ability to phagocytize such aggregates.¹⁶ Neutrophils are also attracted by antigen-antibody aggregates which have activated certain components of the complement sequence. However, these aggregates appear to be more strongly chemotactic for the eosinophil. The unanswered question is, what is the eosinophil doing to the aggregate or, conversely, what is the aggregate doing to the eosinophil?

In the last few years we have gained additional insight into what the eosinophil may be doing. First, consider the distribution of the eosinophil: It spends most of its life span in the tissues and resides only very briefly (a matter of hours) in the blood stream. Hence the tissue pools of eosinophils are enormously greater than those in the circulation. Eosinophils are found in interfaces; that is, they are found at the body surface in contact with our environment. Eosinophils are abundant on the

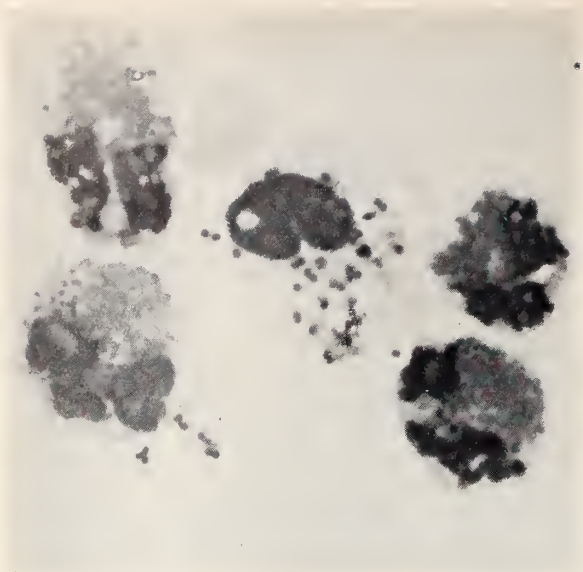


Figure 3.—Neutrophil with many ingested *Staphylococcus aureus* surrounded by comparatively non-phagocytic eosinophils.

gut mucosa, in association with alveolar macrophages at the lung surface, and in the skin. This distribution suggests that the eosinophil may be a first-line defense cell against certain noxious aspects of the environment. Of course, similar suggestions have been made for the lymphocyte in Waldeyer's tonsillar ring and Peyer's patches. It is likely that eosinophils have evolved for a specific purpose rather than being a "phylogenetic carry-over" from more primitive life forms. In all probability, the eosinophil has evolved in higher animals for a specific function which is presumably carried out at interfaces.

In addition, we have noted that eosinophils are attracted by antigen-antibody aggregates. They are not attracted by either antigen or antibody singly but only once the two have formed a complex. The attraction appears independent of the specific antigens involved in the complex and independent of the size of either antigen or antibody. What are the cells doing with these complexes? Clearly they can ingest them; in addition, Archer¹⁷ has published the interesting observation that one can extract from eosinophils substances that antagonize the biological effects of serotonin, bradykinin, and histamine. One may suggest that the eosinophil may be functioning in this regard in order to protect us against the harmful effects of antigen-antibody interactions as well as the pharmacologically active substances generated by such interaction.

The eosinophil is a poor phagocyte in comparison with the neutrophil. I could spend a considerable amount of time documenting this statement,¹⁵ but I would rather show this figure (Figure 3) demonstrating a group of eosinophils and a sole neutrophil exposed to *Staphylococcus aureus*. Obviously the neutrophil, not the eosinophil, has been most effective in ingesting the bacteria. This phenomenon occurs with a number of particles, both bacterial and fungal. The eosinophil simply cannot compete with the faster, more efficient neutrophil.

If the eosinophil is such a poor phagocyte, what then is its function? One observation becomes obvious as one studies eosinophils in tissue culture: With particle ingestion the cell often extrudes its granules intact. One may see intact eosinophil granules circulating in the medium. Is it possible that this granule extrusion plays a role? Is the eosinophil's major function actually not to internalize and digest substances, but rather to release its arsenal into the medium to create an environmental bacteriostatic system or pharmacologic blockade?

In summary, one can consider these possibilities:

- The eosinophil may function to induce bacteriostasis in the environment by extruding its granules, which are rich in cationic proteins and peroxidase.
- Eosinophils prevent tissue injury by antibody-antigen complexes and complement and the associated vasoactive amines and peptides.

What evidence suggests a primary role for these cells in the induction of myocardial fibrosis? To my mind there is no primary evidence that the eosinophils themselves produce tissue injury. All the evidence suggests that they are an epiphenomenon; that is, they are attracted to the sites of myocardial injury which results from another cause. For example, such injury may be induced by a myotropic virus. It is quite interesting that, in an early series of patients with the postmyocardial infarction syndrome,¹⁸ occasionally one had eosinophilia and roughly 20 percent of those patients who came to autopsy had eosinophilic infiltration with spotty myocardial fibrosis. This observation may be one more bit of evidence that eosinophilia is a secondary manifestation of other injuries to the heart.

DR. SMITH: Thank you very much, Dr. Cline. There is time for questions concerning the patient presented this morning or concerning the eosinophil in general.

Martin, could you tell me if other patients have

shown evidence of peripheral muscle involvement by eosinophils such as this patient apparently had?

DR. CLINE: The patients described in the literature often had widespread eosinophilic infiltrations involving lymph nodes, spleen, pancreas and other organs. I have not found a specific documentation of myositis extrinsic to the heart.

QUESTION: Have you found any patients who had lesions similar to those in the heart in the capillaries or in the small arteries of the lung? If so, do these lesions resemble those of periarteritis?

DR. CLINE: No, they apparently are distinct from periarteritis. Patients with eosinophilic carditis may have small vessel involvement in the lung, but this involvement generally lacks the typical nodular features of periarteritis. I might say that only some 45 patients are described in the literature; yet we have had two patients with this diagnosis at this Medical Center in the last four years. Therefore, we must be considered an endemic area.

QUESTION: Are the eosinophils in this disease morphologically different from eosinophils in other kinds of eosinophilia?

DR. CLINE: No, it is extremely rare in any situation to see an eosinophil younger than the myelocyte stage of differentiation. Even in most cases of eosinophilic leukemia, the predominant cell is relatively mature.

QUESTION: The patient presented today had an enlarged heart. Is that typical of this syndrome? What was the cause of the endocarditis?

DR. CLINE: Cardiac enlargement has varied. Often a disparity has occurred between the size of the heart and the degree of congestive heart failure, presumed to result from the constrictive nature of the disease. At least one-third of the patients had cardiomegaly, as in Loeffler's original cases. As to your second question, about the cause of endocarditis, I don't know the answer. I might say parenthetically that the coronary vessels of our patient today were totally patent.

DR. SMITH: I gather that with the exception of the presence of the eosinophil, the terminal pathologic features do not differ very much from those of other types of idiopathic fibroelastosis or cardio-fibroelastosis.

DR. CLINE: Generally that statement is correct except when one reviews the whole series. The fre-

quent right ventricular predominance of fibrosis in eosinophilic endocarditis is rather unusual. In most types of acquired endocardial elastosis, such as that associated with hypertension, beri-beri, and others, I believe that usually the left ventricle is more involved. The cardiologists may be able to clarify that statement. Pathologically, the only difference between eosinophilic and other forms of carditis is the eosinophilic infiltration.

QUESTION: Is steroid therapy useful in this disease?

DR. CLINE: There is no convincing evidence that it is useful. Steroids have been used in only a minority of cases — those recognized since approximately 1950. Generally the reaction to steroids is a transient or sustained decrease in the blood eosinophil level with no clear-cut, beneficial effect to the patient or to his cardiac function. Apparently steroids inhibit the release of eosinophils or increase their turnover in the peripheral blood rather than interfere with their production.*

*Addendum: Since this discussion an additional review of eosinophilic carditis has appeared.¹⁹

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A Retraining Program for Inactive Physicians

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■ *During the past two years a pilot project was conducted in which 19 inactive physicians were retrained in preparation for resumption of active practice. The initial program consisted of a flexible training program of six months to one year patterned after conventional internship-residency concepts. During the second year the program was modified by providing an initial condensed indoctrination period of two months' duration especially designed for this purpose, followed by a preceptor-ship type of training.*

The project was considered successful in permitting trainees to enter some form of active medical work, or to enroll in formal specialty training. The observations made by the faculty of the program and its accomplishments are discussed in the light of the effort expended and the cost of the project.

WITH THE PRESENT shortage of medical manpower, which is expected to become more acute in the future, many methods of increasing the physician pool by means other than training physicians in medical schools have been considered. Among those was the retrieval of fully qualified physicians who, for various reasons, are not actively pursuing medical work. The largest pool of such persons is a group of women physicians who, usually for family reasons, left the medical profession. With the encouragement and financial support of the Manpower Division, Bureau of State Health Ser-

vices, U.S. Public Health Service (later the Physician Education Branch, Bureau of Health Manpower), the Continuing Education Division of the Pacific Medical Center undertook in the Fall of 1966 a pilot project to determine the feasibility of retraining inactive physicians. The purpose of this communication is to report our experiences with this program as well as to suggest means of organizing more efficient future programs.*

Available Facilities

Pacific Medical Center, formerly the Presbyterian Medical Center, occupies the plant that comprised Stanford University School of Medicine before its move to Palo Alto in 1959. It consists of a 240-bed hospital, an affiliated research institute and some ancillary facilities. The hospital had no formal university affiliation until recently, when the Center became a part of the Graduate School of Medical Sciences of the University of the Pacific (Stockton).

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*A model of the retraining program can be obtained from the Physician Education Branch, Division of Physician Manpower, Bureau of Health Professions Education and Manpower Training, NIH, Bethesda, Maryland 20014.

However, it has an active educational program: Some departments offer elective courses for senior medical students from the University of California School of Medicine, and accept students from other medical schools as well. Its graduate training program includes internship (20 interns), residencies in internal medicine, surgery, pathology, psychiatry, neurology, obstetrics-gynecology, orthopedics and ophthalmology, and several fellowship training programs. During the past few years all internships were filled through National Institute of Manpower (NIMP) and most of the residency and fellowship positions were filled. In addition, the Center has an extensive postgraduate program and is among the first 14 institutions formally accredited by the American Medical Association's new accreditation system in continuing education for physicians. The hospital staff consists largely of clinical faculty members of Stanford or University of California schools of medicine and includes some 30 geographically full-time teaching staff members.

The Initial Group

The retraining program was initiated in the Summer of 1966 by two of us (A.S. and F.J.S.). The overall supervision of the program was the responsibility of the Director of Continuing Education (A.S.) who selected a faculty member, geographically full-time at the Center (F.J.S.)—an internist who had just completed residency training and a fellowship in cardiology, and who was budgeted to spend 33 percent of her time on the project. In approaching the retraining program, it was realized that this was to be the first formal program of this kind in existence and that there were no precedents as to plan of instruction or curriculum. Several basic decisions were made before the inception of the program: (1) It was to be a practical clinical traineeship of at least six months' duration, with trainees spending preferably full time in training (40-hour week), although provisions have been made for some trainees attending part-time, but not less than 20 hours a week. (2) The core of the training program will be internal medicine, followed by elective brief rotation through specialty services. Only those who have attained board certification or board-eligible status would be given straight specialty training. (3) Trainees were not to be given primary patient responsibilities and were exempt from after-hours and night "on-call" service.

Recruitment

A list of women physicians not in practice was obtained through the Bureau of Research and Planning of the California Medical Association from the master tape of the AMA. The list revealed 67 such persons within the San Francisco Bay Area counties (population 4.6 million). Each physician in the area on the list received a letter-questionnaire asking whether such a training program would be of interest to her. Forty-five answers were received, 33 expressing interest. A follow-up letter sent to the 33 interested women described the proposed program and indicated readiness to accept applications. Six women physicians indicated willingness to start training at once. They were interviewed, were found acceptable, and constituted the first class of trainees. Two more enrolled later during the first year.

Analysis of the trainees

The first class, which began training in September 1966, consisted of eight students, ages ranging from 39 to 57, who had been away from training or active practice for five to twenty-two years. All trainees were married (two widowed). Six of the eight had children. Ages of children ranged from 18 months to adulthood, family size from one to five children. The original graduate training of the candidates ranged from completion of internship (one) to board certification (two, a pediatrician and a radiologist). Graduate training included rotating internship and residencies in internal medicine, anesthesiology, psychiatry and surgery, in addition to the certified specialists.

Planning and initiation of the program

Before commencement of the training program the objectives and plans of training were discussed in detail with the chiefs of services and members of the house staff. The background and estimated amount of guidance the trainees would need were discussed. The hope was expressed that the interns and residents would participate actively in the teaching program. It was made clear that the addition of the trainees to the ward staff should in no way infringe on the teaching opportunities of the house staff. The program, when presented in this fashion, met with interest and enthusiasm by the attending and the house staffs alike.

Each new trainee was met with individually to discuss prime objectives of retraining. With the information thus obtained, we tried to design indi-

vidual programs which would fit best the needs and objectives of the trainee.

Early in the training, both the trainees as well as the supervisors recognized the limitations imposed by prolonged absence from practice as well as differences in background, age and future plans. Necessity for more intensive training in limited fields also became apparent. The two board-certified specialists were trained in the respective fields. The pediatrician had exclusive retraining in pediatrics; arrangements were made to provide her with training in other institutions than our own in those areas of pediatrics where our material was inadequate. The radiologist obtained retraining full-time in the department of radiology, but at her own request was included in general training in internal medicine for a period of one month.

A third candidate had four years of training in general surgery but lacked one more year for completion of her training. She spent her initial two months in the department of medicine and then the remainder of her time in orthopedic surgery (as a possible step toward formal training in this field in the future). Candidates who were not sure about the type of medical work they might wish to do in the future were assigned to the department of medicine and were initially given ward service training. Five trainees started their rotation on the medical wards. Three of them, two with background of general practice and one of internal medicine, planned to resume practice in offices or hospital outpatient clinics dealing primarily with adult patients. Their rotation, after exposure to internal medicine, included such outpatient clinics as gynecology, dermatology and otolaryngology, as well as rotation through the Emergency Room service.

The fourth trainee had worked in the past in an emergency hospital and wished to resume similar work. Her training included internal medicine, followed by assignment to the Emergency Room. The fifth trainee had worked as an anesthesiologist up until about 20 years before commencement of retraining. Her objective was to work in gynecological office practice, for she developed interest in that field. Her training included internal medicine, followed by prolonged assignment in the gynecological clinic.

All trainees were required to attend the formal teaching sessions for the house staff (teaching conferences in the various specialties, basic science lectures, clinicopathological conferences, tumor

boards and the like), and were encouraged to attend postgraduate conferences given by this institution which took place two to three times a month, usually on Saturdays. Arrangements were also made to admit the trainees to suitable postgraduate courses offered by the University of California School of Medicine, San Francisco. In addition, a series of lectures designed specifically by the trainees were given by staff members of this hospital. A list of recommended reading, consisting of texts and review articles, was given to trainees.

Changes in Curriculum

The first year's curriculum was considered experimental and observations concerning its effectiveness were made continuously. The initial curriculum was designed along conventional lines of graduate medical education—that is, a modified internship-residency type of retraining. The advantages and disadvantages in utilization of this system became apparent within the first few months of the training program. On the positive side, inactive physician-trainees constituted a well-motivated, knowledge-hungry group of students who on the whole were more mature than the average intern and resident. Absenteeism was virtually non-existent, and attendance at voluntary teaching sessions, such as weekend courses for practicing physicians, was very high—a decided contrast with the house staff. On the negative side, most trainees had an initial lack of confidence; there was a reluctance to assume responsibility for patients. A need for a more systematic review of material once learned—physical diagnosis, differential diagnosis, use of laboratory tests and modes of treatment—also became apparent.

On the basis of our experience with the first class, the following new curriculum evolved for the second year of our project. An initial indoctrination period was organized, during which didactic instruction specially designed for this group was given. "Headquarters" were developed, namely a combination conference-study room for these special students. A half-time coordinator was recruited among graduates of the first class (M.B.). A systematic review of newer modes of diagnosis and treatment was developed and consisted of lectures, roundtable discussions, and teaching films and tapes. Orientation in ancillary hospital services—social service, nursing, medico-legal matters, physical and occupational therapy—was in-

cluded. In addition, a small library of books and reprints, specially designed for the re-trainees, was housed in their conference room.

The second class began in October 1967 and included five trainees, plus one carry-over trainee from the first class (she had begun her training late during the first year). The new group included one man who had been away from medical work for a number of years. Ages of the new students ranged from 30 to 60 years; graduation dates 1936 to 1962. Time away from practice ranged from five to twenty years. Individual rotation, taking into account earlier training and future objectives, was applied to this group, as to the first one. In January 1968, budgetary cuts of the USPHS contract required a reduction of the trainee stipends to one half. This was accepted readily by all trainees. In May 1968, a third class was initiated for a four-month training course (five trainees). This group received no stipend at all. The curriculum followed closely that developed for the second class.

Follow-up

Of the initial group of eight trainees all obtained medical positions as follows: two work in a medical office—a surgeon and a gynecologist; two are full-time physicians in a hospital out-patient department; the two specialists resumed specialty practice—radiology and pediatrics; one enrolled in a residency in physical medicine and rehabilitation at a medical school and one works for the State Welfare Department.

Discussion

This training program, in addition to offering 19 persons the opportunity for reentry into medical work or updating their knowledge, permitted us to review at first hand the needs of such a group and to visualize the kind of program which would be ideally suited to fill these needs.

It should be realized, first of all, that medical re-trainees constitute a widely heterogeneous group of persons with wide variation in personal motivation, background of knowledge, age, physical stamina, length of previous training and time away from practice. It is clear that the existing conventional training programs, such as residency or postgraduate courses, are seldom suitable for such persons, at least initially. Flexibility in the total program appears to be an important prerequisite of a successful program. It is our impression that a cur-

riculum specifically designed for such persons is imperative. Such a curriculum should consist of two phases: Phase 1, an intensive review course in basic aspects of clinical medicine; Phase 2, a program of supervised patient contact with gradually increasing assumption of patient responsibility. The first phase belongs in a major medical center—either a medical school or an institution with an active postgraduate program. Such an institution, in undertaking a program of retraining, should devote enough thought, funds and energy to work out a specially designed program, rather than attach it to existing teaching functions. The second phase might be undertaken by a smaller teaching hospital, provided its faculty has the motivation and understanding of the problem involved in conducting it.

The recruitment of students requires careful planning. Our experience indicates that a direct approach by letter or questionnaire of the pool of inactive physicians provides a small yield—less than 10 percent. In selecting the candidates for retraining, the most important points appear to be the psychological makeup, adequate general health, and assurance of plans to assume some medical work. It is important to note that the great majority of candidates for retraining are geographically tied to an area by virtue of a husband's job and responsibility; and many have home responsibilities that make part-time programs preferable. Our experience had demonstrated that availability of stipends, while not a prerequisite for enrollment, does constitute an important inducement, particularly for those whose standard of living makes the addition of a housekeeper a financial hardship. Therefore, availability of selective, rather than routine, scholarship funds appears to be highly desirable in initiating such a plan.

The expense of running such a program is considerable. In the first place, trainees are unlikely to be able to pay tuition—they may even need subsidy. Secondly, the program is too complicated to be run by volunteer faculty. Our program provided funds for a coordinator who devotes one-third of his time to the job and who later was assisted by a half-time instructor. In addition funds are provided for a modest number of lecture honoraria. Such a core faculty was adequate for a demonstration project, but would have to be enlarged, if a continuous, routine program were in existence.

The initial phase of retraining—the re-indoc-trination phase—may be condensed into an intensive course of six to eight weeks. As was previously stressed, such a course belongs primarily in a major medical center, preferably in an institution with major interest in continuing medical education. While such courses would be primarily designed for the reactivation of physicians who have been away from medical contact, it could also be used with some modifications for updating practicing physicians. Whether such courses were to be given once a year, or at more frequent intervals, would depend on the number of applicants. It would probably be most economical to have not more than four or five such courses given at widely scattered geographical locations over the West Coast, Midwest, East Coast and the South in areas where the largest pool of inactive physicians is known to exist. It is assumed that such a short course could be attended by a woman physician some distance from home in spite of family obligations, provided that a longer retraining of Phase 2 would then be found in a location near her home. Such a course could be sufficient to prepare those trainees who so desire, to enroll in a formal residency training in lieu of the specially designed Phase 2 of retraining. Such formal training would be made more attractive if a half-time residency (one year of training extended to 24 months) were made available. Such a plan has been experimented with in some fields in the Boston area in response to a pilot study by the Radcliffe Alumnae Association.

Perhaps the most important question related to the project is whether the expense and the effort

of organizing such a program is worthwhile. Our study has shown that only a small fraction of potential candidates for retraining took advantage of the offer—even with the inducement of financial support.

Undoubtedly, the more strongly motivated re-trainees would have found other means for returning to medical work. Nevertheless, a program especially designed for such a purpose by individuals who have given a great deal of thought to the program unquestionably increases the probability of producing a better end-product. While the most obvious pool of inactive physicians is women who have family obligations, other members of the medical profession could also be retrained and become better prepared for active medical work. Among the latter are physicians who retire from the Armed Services Medical Corps and who spend some years in medical administration, those who interrupted medical work for reasons of health or those who may have had their medical license temporarily suspended. Furthermore, such programs may be more suitable for many foreign-trained physicians aiming at settling in this country than an internship at a hospital with minimal teaching facilities. Finally, it should be pointed out that in some European countries, entirely independent postgraduate schools of medicine have been very successful, such as the Royal Postgraduate Medical School of the University of London. Postgraduate institutions have, generally, not been too successful in our country. This program may be more suitable to a postgraduate school than a medical school, whose major responsibility is to train undergraduate students and provide graduate training programs.

EDITORIAL

Professional Liability And Patient Care

THE ESCALATING COST of professional liability insurance which practicing physicians in California must bear reflects a situation which can only have profound effects on the quantity, quality and cost of patient care. The problem is underscored at this time by the fact that thousands of physicians had their premiums a little more than doubled, beginning first of October, and for some specialists these premiums amount to several thousands of dollars a year. The number of malpractice suits is increasing, the costs of litigation are rising, some of the awards are becoming astronomical (there are several over a million dollars), and quite understandably there is a notable lack of enthusiasm in the insurance industry to rush into this sort of business, particularly when carriers have no sure way of knowing how long after an incident a suit may be filed or what the going rate for awards may be when it is settled.

The causes of all this are complex. Physicians know that there is a risk of untoward reaction or a poor result in almost everything they do, no matter how well they do it. It is true that as science advances and new and better treatments become available, these are often more dangerous and carry greater risks. Yet when an unfortunate result occurs, the courts are apt to hold "the thing speaks for itself" (*res ipsa loquitur*) and the defendant physician finds himself in the factual posi-

tion of being guilty unless he can prove himself innocent, which seems somewhat unfair in these days when the presumption of innocence for even the manifestly guilty is so high on the legal agenda. There also seems to be a growing feeling abroad that everyone has a right to be healthy, that medical science now knows enough to make everyone healthy, and that when there is a failure it must be someone's fault. Experience shows that this approach can be costly. The traditional reluctance of patients to sue their physicians and the erstwhile reluctance of juries to hold the physician responsible when an unfortunate incident occurs, because he "tried to do his best," is becoming a thing of the past. We are living in a new era when the right to sue is being fully exploited by the public. One can only speculate concerning how much the peculiarly American custom of contingency fees for plaintiffs' attorneys may have to do with it.

There is no question that when a physician truly commits malpractice the unfortunate patient should receive fair compensation insofar as this is possible. This is the position of the medical profession, which long ago took steps to make qualified disinterested physicians available to testify in behalf of plaintiffs and so negate the so-called "conspiracy of silence." Through the mechanism of review and advisory committees medical societies have sought to determine if malpractice was actually committed as the plaintiff claimed, and, if there was malpractice, recommend that the suit be fairly settled, and if there was no actual malpractice that it be fought. There have also been many programs to reduce the causes of malpractice and of suits, the most recent being the highly successful "California Invitational." For several years the California Medical Association has sought relief through the Legislature, this in the public interest as much as for the physician. The first successful

effort resulted in the "Good Samaritan Law," and other bills subsequently enacted have extended the principle of this law. Last year the Legislature passed several new laws dealing with the statute of limitations, privileged communications for medical society and hospital staff committee proceedings and records, and advance payments to an injured patient, without presumption of guilt, all of which were helpful. An experiment is being tried with prior agreement to use arbitration. There is talk of something like "trip insurance" whereby insurance against a bad result would be purchased by the patient at the time of each hospital admission. There is discussion of a possible limitation on the extent of the professional liability of physicians, as is now the case with the liability of employers in industrial accidents. And it is intended that independent actuarial analysis will be sought of the underwriting experience, claim and loss projections and premium structure of all the principal professional liability carriers in the state, as has already been done with some.

But the escalating costs of professional liability insurance continue to race ahead of all these worthy efforts to control them. The impact upon the quality of patient care and its cost is now becoming serious. On the positive side there is no doubt that the ever-present threat of suit has tightened up many procedures and practices. But it has also led more and more to what has been called "defensive medicine," that is, those things a physician does or does not do in order to lessen his risk of being sued. The things the physician *does*, in this regard, often unnecessarily increase the cost of health care, and those he does not do may well deprive a patient of an opportunity to receive the latest and best in scientific care simply because the risk is more than negligible. Also on the negative side, it is obvious enough that all the costs of litigation and awards are ultimately paid by the public, although this basic fact is accepted reluctantly or not at all in some quarters.

In a larger sense some of the predictable effects on health care delivery may prove even more serious. For example, young physicians may begin to seek alternatives to starting in private practice because of an unbearably high cost of the professional liability insurance which they must have even before they can see a patient. And, even worse, what will be the action taken by physicians already in practice if the cost becomes prohibitive or if they are no longer able to get any insurance at

all? This would mean that they would have to assume a personal risk of an adverse court judgment which might be for a million dollars or more. This is not mere speculation. There is already good evidence that a substantial number of physicians are beginning to take shelter from these problems, from the irritants of government interference with their practice and from other deterrents to fulfilling a personal direct responsibility for a patient's care, which is the very core of private practice. These physicians, often among the most capable, are seeking other avenues for their professional fulfillment. The lesson is too slowly being learned in a number of quarters that physicians are very much like other people. They go where the incentives are and avoid the deterrents.

The eventual effect of all these current trends upon the quality and quantity of patient care is impossible even to estimate. The forces described are among the many which could easily lead to the destruction of personal direct physician responsibility for individual patient care. It is hard to guess what the ramifications of this might be for the profession or for society, but it is equally hard if not harder to imagine how in the world the patient might ultimately benefit. The medical profession is doing all it can. Perhaps the time has come to give it some real help.

Management of Diabetic Coma

THE ARTICLE BY Gwinup and Steinberg in the current issue of this journal (page 347) treats an old subject in a modern way. A few points brought out by these authors deserve some additional comment.

Whereas diabetic coma was the first cause of death in persons with diabetes before the advent of insulin in 1921 and practically always terminated the lives of juvenile diabetics, any fatal outcome today must be attributed either to complicating factors or inadequate therapy. There is, unfortunately, still too much of the latter, as suggested by the variation in mortality figures of 25 to 2 percent in different reports.¹ This is chiefly referable to poor therapy and the differences in know-how between one group and another.

Many cases of diabetic pre-coma are really "intercurrent ketoacidosis" and are found frequently in insulin-dependent diabetics, being most prominent during the teen age. These patients are easily handled by readjustment of their insulin and being careful to continue carbohydrate intake, if anything at a higher level, and if necessary by vein, since inadequate utilization of glucose invariably leads to mobilization of free fatty acids and subsequently to acidosis.

The more severe cases of diabetic coma, however, are those accompanied by CO_2 -combining power below 15 mMoles of CO_2 per liter. At this level pronounced drowsiness is observed but coma does not usually ensue until levels below 10 mMoles per liter are reached. One then deals with coma.

The first duty of any physician is to *prevent* diabetic ketoacidosis and coma. Most often the patient's self-neglect is at the root of the trouble; he may omit his insulin, starve, or fail to deal adequately with undue metabolic stresses such as annoying experiences, anxiety, infections, and severe trauma. All of these require increased insulin intake. It is the education of the patient and family on how to avoid these preludes to diabetic coma that is all-important. Most often this is left to ancillary personnel such as nurses, social workers, and neighborhood friends who do not always do justice to this all-important precautionary matter.

Once typical symptoms have appeared, there is too often a *delay* in diagnosing and initiating treatment. Every case of severe diabetic ketoacidosis with impending coma must be considered an emergency and the patient admitted to hospital for immediate treatment in the emergency room and continuous monitoring.

As pointed out in the article, the *diagnosis* can be made promptly by the use of bedside procedures such as Dextrostix® (Ames) and Acetabs® (Ames). However, one must then draw blood for baseline determinations in the clinical laboratory before starting therapy. Normal ketone bodies with a high blood sugar are characteristic of the relatively recently described syndrome of *non-ketotic hyperosmolar coma*,² treated with much insulin and hypotonic fluids of neutral pH. In contrast, normal ketone bodies with only moderate, if any, elevation of blood sugar, but with signs of pronounced acidosis (such as deep hyperventilation) point to *lactic acidosis*,³ requiring treatment with bicarbonate. In addition to determining glu-

cose levels and ketone bodies at the bedside, a complete blood count, preferably with a hematocrit, is necessary for evaluation of hydration during treatment. One should not be led to assume that there is severe infection by finding leukocyte counts above 12,000 per cu mm of blood with a shift to the left in the differential. This is part-and-parcel of ketoacidosis per se. An electrolyte panel and electrocardiogram before therapy are essential. A serum creatinine determination is useful for evaluation of the degree of renal impairment, often quite reversible.

Insulin therapy consisting of crystalline insulin must be started immediately and vigorously. The intravenous route is preferable to subcutaneous at first, especially if there is a degree of shock. With a severe coma, 100 units must be given half-hourly. The induction of hypoglycemia at the onset is practically impossible. In contrast, giving insulin "too little and too late" has accounted for many a fatality.

For *shock* one often uses albumin, and rarely one must use blood as well as large amounts of 0.45 percent saline solution. This is used rather than 0.9 percent isotonic sodium chloride solution since these patients are decidedly dehydrated and hyperosmolar. Next, one must concentrate on improving the prevailing *acidosis*, which may be inferred from the low CO_2 -combining power or by finding a decreased pH. Ordinarily this will be below the normal of 7.4 and closer to 7.0. Since the action of insulin is decidedly impaired by the acidosis, it behooves one to raise the pH into the range of 7.3 to 7.4. This cannot be achieved promptly by the use of 1/6 molar sodium lactate since it must be metabolized before the sodium becomes readily available. The same is true of sodium chloride, which can counteract acidosis only after the chloride has been excreted into the urine; this takes time and good kidney function. Thus, it is preferable to use sodium bicarbonate, adding one to three vials of 44 mEq each to the 0.45 percent sodium chloride infusion. One cannot overemphasize the need to start adding *glucose* to the intravenous fluids as soon as the blood sugar level has reached between 200 and 300 mg per 100 ml. This will allow for the reduction in ketone bodies which insulin alone cannot do effectively. Soon afterward, *potassium* must be started in the form of 20 to 40 mEq per liter as potassium chloride or preferably basic potassium phosphate. The former is slightly acidifying; the latter acts as a

buffer and supplies both potassium and phosphate, which are used in the deposition of glycogen in the liver and in the utilization of glucose in the periphery. The failure to add potassium to the regimen may result in a fatal vascular collapse after eight to twelve hours of therapy, due to cardiac arrest.

It is most important for adequate therapy of diabetic coma to be aware of the danger points that might lead to a fatal outcome. Acute *gastric dilatation* may be dealt with by evacuating the stomach, and lavage with sodium bicarbonate before starting insulin therapy. An *inadequate dosage of insulin*, especially when given subcutaneously rather than intravenously with the patient in shock, leads to central nervous system depression and either continuation or recurrence of coma. *Sudden cerebral edema* during therapy is particularly likely to occur when a fall in blood sugar and a rise in pH have been induced too rapidly. This is found to be accompanied by atrophy of the central nervous system due to anoxia and the changes in the extracellular fluid composition. In general, when the blood sugar level in the plasma and extracellular fluid is lowered, it leaves the cerebrospinal fluid glucose still elevated, and this will lead to increasing edema of the central nervous system. An abnormal pathway for glucose metabolism in the CNS leading to sorbitol deposition has recently been implicated as another causative factor. Finally, *hypokalemia* with cardiac irregularities and arrest is a late complication that can be completely prevented by giving potassium. However, one must guard against starting this too early, since usually at the very onset of diabetic coma, especially with acidosis, there is an elevation of serum potassium and adding more can lead to cardiac arrest with hyperkalemia. Lately a few cases of low potassium at the onset have been described⁴; they are very rare. Fortunately, the electrocardiographic changes between these two extremes are quite different; thus, one can differentiate even before the laboratory determinations for potassium are available.

To assure a favorable outcome of diabetic coma, one must consider the therapeutic attack at three levels: First, one must control shock and dehydration. Second, one has to rapidly reduce ketoacidosis and hyperglycemia. Third, one has to be aware of secondary *hypokalemia* and rarely hypoglycemia. There is a finite mortality, even now. The total prevention of this occurrence can be

achieved only by careful, repeated education of the patient and family. They must be warned never to forego the insulin injection, while providing (if necessary) carbohydrates by small sips of sugar-sweetened tea or fruit juices between attacks of nausea and vomiting. In this fashion, the worst type of ketoacidosis can be prevented. Since therapy has to be rapid to be effective, one should prepare for this emergency by having the insulin and the different solutions readily available for a day that we hope will never come.

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Phlebotomy Treatment Of Porphyria Cutanea Tarda: Is It Really Effective?

PORPHYRIA CUTANEA TARDA (PTC) is the most commonly recognized form of porphyria. The term *porphyria cutanea tarda* was first offered by Waldenstrom in 1937¹ and included all forms of porphyria with cutaneous lesions other than congenital porphyria (Gunther's type). It was not until 1954 that Schmid, Schwartz and Watson² proposed that a "cutanea tarda type" of porphyria without any other manifestations be recognized. At about that time, reports from England and South Africa emphasized the constant high fecal excretion of protoporphyrin and coproporphyrin in many patients with cutaneous porphyria, and currently the term *variegate porphyria* is applied to that familial type of porphyria with both cutaneous disease and acute porphyria attacks. Porphyria cutanea tarda, on the other hand, is a purely cutaneous disorder, characterized by a pronounced

increase in urine and fecal uroporphyrin of hepatic origin, no increase in urine porphobilinogen and, in contradistinction with variegate porphyria, fairly normal fecal protoporphyrin excretion.

Most of the earlier descriptions of PCT emphasized a high frequency of frank liver disease, usually alcoholic cirrhosis. A larger experience, however, now indicates that cirrhosis is not common among PCT patients. Eales noted abnormal BSP retention in only 23 percent of PCT subjects in Cape Town.³ In our own experience, cirrhosis has been present in fewer than 10 percent of patients. On the other hand, a fairly heavy intake of alcohol is common.

Until the early part of this decade, no treatment, other than interdiction of alcohol, was being seriously offered to the PCT patient. Following the initial communication by Ippen, in 1961,⁴ a number of enthusiastic reports have now appeared relating remission of PCT to repeated phlebotomy. This therapeutic approach followed the recognition of frequent high values for plasma iron and hepatic siderosis in PCT patients. Elsewhere in this issue (page 357) there is an additional report by Dr. Herschel Copelan, suggesting that remission in a PCT patient was induced by the removal of 4,600 ml of blood over a period of five months. It is always hazardous to draw any conclusion from a single case therapeutic experience but a sufficient number of cases treated by phlebotomy have now been reported to be impressive. If phlebotomy treatment for PCT is effective, the reason for its effectiveness is not so clear.

An overwhelming amount of evidence is available demonstrating a high incidence of hepatic siderosis in PCT patients. Descriptions of liver biopsy material, reported from many parts of the world, have shown excess iron in both parenchymal and Kupffer cells in nearly 75 percent of PCT subjects. Elevated values for plasma iron and, more particularly, saturation of circulating transferrin are also commonly observed. As pointed out by Kalivas et al,⁵ the degree of hepatic siderosis, when present, although variable, is usually not pronounced and is more of the order observed in alcoholic cirrhosis with hepatic siderosis than that observed in classic haemochromatosis.

In many patients, the iron overload may be related to the heavy alcohol intake. In some patients who have consumed no alcohol, a history of heavy iron ingestion, usually as an iron-containing vitamin preparation taken over many years, can be

elicited. Among Bantu subjects in South Africa, PCT is common and hepatic siderosis is also common, presumably from drinking the notorious "Kaffir beer," containing large amounts of iron. We and others have observed PCT with hepatic siderosis in elderly men receiving estrogen therapy for prostatic carcinoma. Welland and Carlsen reported an eight-year-old boy with "PCT" and hepatic siderosis who had taken oral ferrous sulfate for two years.⁶

In spite of the frequency with which hepatic siderosis is observed in association with PCT, any causal relation between hepatic iron and hepatic uroporphyrin synthesis has not been demonstrated. For example, patients with classic haemochromatosis or alcoholic hepatic siderosis do not show any evidence of disordered uroporphyrin metabolism. PCT has traditionally been considered to be an acquired disorder with an idiosyncratic background and it is possible that against this idiosyncratic background, environmental factors, such as iron, alcohol and estrogens, either alone or in combination, may precipitate the disorder of uroporphyrin metabolism. In this light, the report by Welland et al⁷ of PCT in one of identical twins is of interest. Only the involved twin had taken oral iron and showed excess iron in liver biopsy tissue. Also, we have observed PCT to develop in a patient with a refractory anemia after he had been heavily transfused and had acquired pronounced hepatic siderosis.⁸

Quite obviously, it has been attractive to attempt to treat a disorder so frequently associated with iron overload by phlebotomy; and many reports, including Copelan's current case report, describing remission following repeated phlebotomy, have now appeared. As is so often the case with a new therapeutic approach to a problem, it is disappointing to recognize that no investigator has seen fit to subject phlebotomy treatment of PCT to a controlled trial. This critique is particularly germane to PCT since biochemical and clinical remission can well occur without phlebotomy, especially in the alcoholic patient who stops drinking. Nevertheless, it is impressive to observe virtually complete biochemical remission following the removal of 2,000 to 4,000 ml of blood in a patient who has had PCT for a number of years.

If phlebotomy is an effective treatment for PCT, the question that must then be asked is how it works. It is probably deceptively logical to assume that the simple removal of iron from the liver

affects hepatic uroporphyrin metabolism. It should be reemphasized that not all patients with PCT have evidence of iron overload or hepatic siderosis. Nonetheless, such patients also appear to benefit from venesection. Protracted remissions have been observed in a few PCT patients who had received chloroquine, and liver biopsy specimens during remission showed the same degree of hepatic siderosis as before the chloroquine was given. If the effect of phlebotomy is not related to iron removal, then one can only speculate as to alternate mechanisms. Certainly it is unlikely to be the removal of porphyrin, per se, since the amount of porphyrin withdrawn in the course of often repeated phlebotomy is minute compared with the uroporphyrin excretion in a single day. Other factors, critical to the abnormality of uroporphyrin metabolism characterizing PCT, might be removed during phlebotomy and might be very slow to reaccumulate, particularly if predisposing influences such as alcohol were also then discontinued. It should be pointed out that when alcohol, estrogens and iron ingestion seem to be related to PCT, there is invariably a long history of this exposure, usually years, before clinical PCT develops. In this sense, it is of interest to note that with continued alcohol intake the patient reported by Copelan did have

a striking increase in uroporphyrin excretion again, three years after the phlebotomy treatment.

The uniformly good response to phlebotomy among PCT patients probably attests its validity even though a controlled trial has never been done. However, the mechanism for this effect remains unclear in spite of the superficial evidence that iron removal is involved. A controlled trial, randomizing patients for removal of only red cells versus removal of only plasma, might well answer some of these questions.

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COMPRESSION TO PREVENT THROMBOPHLEBITIS

"One effective method for preventing thrombophlebitis is to apply compression bandages to the extremities in all individuals who are in bed. Compression bandages do two things. They increase the blood flow through the deep veins by compressing the superficial veins and shunting the blood from the superficial veins into the deep veins. But I think even more important is the fact that the compression bandages act as an insulating agent. . . . We've observed . . . that among individuals with fractures of the lower extremity, those who are treated by extension have an extremely high incidence of venous thrombosis whereas those . . . who are treated by encasement in plaster have an extremely low incidence of thrombosis. Both groups of patients are immobilized; but in those who are immobilized in plaster, the plaster represents an insulating agent retaining the heat of the extremity and increasing the blood flow in the extremity."

—ALTON OCHSNER, M.D., New Orleans

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LETTERS to the Editor

The Physician, His Association And Health Care

To the Editor: Not long ago there was a most provocative series of articles that ran for several months in CALIFORNIA MEDICINE entitled "The Scope and Responsibility of Medicine."¹ Many of the thoughts expressed have been further emphasized by the appearance recently in the *New England Journal of Medicine* of two articles^{2,3} relating to organizational changes and/or new bodies which might define health problems and work toward solutions more efficiently than our existing organizations. One article, written by Dr. F. J. L. Blasingame, details ways in which the American Medical Association might alter its structure and become functionally more responsive. Another, by Dr. James A. Shannon, details some of the early history of a small group trying to establish a National Academy of Medicine, working mutually with the National Academy of Sciences and the National Academy of Engineering.

It is apparent that many of the problems and paradoxes now existing in the distribution of health care in this country are crying for solution by the alteration, resurrection or creation of new structures for this purpose. An editorial, "Treatment for the Medical Body,"⁴ in the *New England Journal of Medicine* states: "The practicing physician, in turn, must aggressively seek a role. If his attitude and that of the organization that represents him is negativistic, he once again may opt out in the shaping of plans that influence his own future."

When the physician, overworked and overstressed in fulfilling his obligations, becomes part

of an association, the role of that association becomes in many respects the voice of all physicians. The association assumes responsibilities over and beyond those of any single physician to his patients. It now has a certain responsibility for care given by *all* physicians that belong to it.

Some aspects of health care seem uniquely and appropriately within the purview of such an association, particularly if it expresses the vast majority of practicing physicians. First of all, perhaps, is the encounter that takes place between a practitioner and his patient. The role that this encounter plays in health care has not perhaps been adequately studied but is certainly a most proper concern of the physician's association. Also, his association should be involved with other disciplines that impinge upon the care of his patient, at least when they affect the welfare of his patient or the therapeutic process by which he is taking care of his patient. The physician's association should be intensely interested in all phases of physician education, from the time a student in college decides to become a physician and begins studies oriented in this direction, through medical school, and on through his entire professional life.

Next, the association must—as an association—take cognizance of the way in which health care is given to the people of the land in which it operates. Thus, the American Medical Association should have a deep interest and a strong voice in the definition of standards for the delivery of health care.

Finally, the association should be attentive to the application of biomedical research to patient care.

It seems that the above points represent those areas central to the activities of an organization such as the American Medical Association. Certain other activities are of obvious interest to the organization but they are areas over which it can have lesser degrees of control. Financing of care might be considered as one of these. While opinions may be rendered, the mechanisms by which people pay for their care are largely not in the

control of the association to which physicians belong.

The growing professionalism of allied groups—nurses, social workers, hospital administrators, etc.—and the necessity to weld them into a smoothly working team for the best care of patients, while a deep concern of a physician's organization, is a difficult one for it to influence.

The role of government as a supporter and regulator of ever-increasing aspects of medical care is similarly of great concern but, again, lesser control.

Decisions regarding these vexing problems are generally made by public bodies after consultation. Much of the uproar that is now current with respect to the roles of the American Medical Association, the American Public Health Association, the American Association of Medical Colleges, etc., revolves around the selection of the consultant. Should it be a group of prestigious medical scientists, teachers, educators and administrators—such as is proposed for a National Academy of Medicine—"free from special interests"? Should it be the American Medical Association? The American Hospital Association? The American Association of Medical Colleges? The American Nurses' Association? The list can be expanded indefinitely. Should we, as physicians, want our American Medical Association to enlarge its membership by acceptance of workers of all types in health care? Should we have a large, representative but diffuse organization, or should the American Medical Association remain responsive to and representative of physician needs and then be amply represented in a broad "American Health Association" composed of other institutional representatives?

It is almost axiomatic that any solutions achieved to cope with the problems of health care in this country will carry within them the seeds of further problems. In solving the problems we have now, there must be developed a mechanism by which the problems of the future will be met flexibly and easily. It seems to me a problem of this type is more efficiently handled by a federation of organizational representatives than by one reconstructed out of a former organization or a body made up of people with no special interests.

It seems to me, as a physician, that the broad and deep problems which concern physicians and physicians' organizations represent many reasons for keeping the American Medical Association a

physician-oriented group. The association, whatever the reorganization that may take place in it, should still confine itself to the problems which are related to physician activities. At the same time, the American Medical Association should join with other organizations in the development of a broadly based group within which the various health care disciplines can meet and can discuss and can work. The development of an organization of this sort would mean no lip-service development. This should be a large representative body, capable of hard work, representative of wide opinions, with good lines of communication to and from the various organizations which it represents. It should be sufficiently funded to carry on extensive day-to-day activities, as well as the types of surveys and data collections necessary for the achievement of adequate opinions. While the economy of time achieved by the creation of a single-minded group which would—through sheer force of persuasion—solve some of today's problems might be an attractive feature, this might be at the cost of the flexibility needed for future problem-solving. The somewhat slower and more cumbersome arrangement achieved by an open, democratically-oriented federation composed of organizational representatives of the health professions would, in the long run, be a more truly representative body for health care in America.

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Cystic Fibrosis in Children And Adolescents

To the Editor: My recent article, "Psychological Aspects of Cystic Fibrosis in Children and Adolescents," in the May 1969 issue of *CALIFORNIA MEDICINE* resulted in such a deluge of requests! I was surprised to find how much interest there is

in the psychological aspects of cystic fibrosis. Dr. Holsclaw's letter is important, and I wonder if you would include it somewhere in your journal because I think it would be of interest to the many readers who have expressed their absorption in this topic.

JOSEPH D. TEICHER, M.D.

(*Dr. Holsclaw's letter follows.—Editor*)

Dear Doctor Teicher:

I recently had the opportunity to read your article, "Psychological Aspects of Cystic Fibrosis in Children and Adolescents," which appeared in CALIFORNIA MEDICINE, May 1969. I want to compliment you on an excellent summary of a very broad and exceedingly difficult subject. I would suspect that as a result of this publication, you will

be called upon in the future to speak about this subject at various conferences, etc. I would like to urge that you include in future presentations some comment about the male sterility which has been recently discovered. As you can well imagine this places an additional psychological burden on the male adolescent with cystic fibrosis. It would seem to me impossible to not have some effect on the adolescent male self-image as well as his projected plans for future marriage and family. I suppose this is a mixed blessing, however, in the sense that the male sterility may be nature's contraceptive. This would lend even further emphasis to your closing paragraph concerning the adoption of children by persons with cystic fibrosis.

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DELAYING REPAIR OF RECTOVAGINAL FISTULA

"The rectovaginal fistula is a distressing complication for both the patient and the surgeon. Here I'd like to raise a red flag because there's a great tendency to press for immediate repair, and it seems to me that this is in error. To avoid the possibility of having the fistula recur after the initial attempt to close it, the part of wisdom is to delay that repair until the infection has quieted down. Remember you cannot judge the extent of damage to the rectum by the size of the vaginal opening. The one in the rectal wall is always bigger than the one that you see in the vaginal canal. If it's a particularly large fistula, you may have to wait as long as six months. Usually, they're associated with infection. Unfortunately, the antibiotics are not as useful as you'd like to have them in clearing up any fistulous abscess. So it may be advisable to perform a temporary colostomy—a diverting colostomy . . . with no spill over. In this way, you minimize the contamination for the fecal stream and have some chance of clearing up this infection before you start any attempt at repair. Now whether you do a colostomy or not depends on the extent of the damage and the chances of eliminating the sepsis by any simple means that you might employ.

—LANGDON PARSONS, M.D., Boston

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Prosthetic Replacement of the Aortic Valve: A Current Assessment of Operative Results

ANDREW G. MORROW, M.D.

Material Supplied by the California Heart Association

IN THE ADULT PATIENT with clinically significant aortic stenosis or aortic regurgitation, the aortic valve is always severely deformed, frequently lacking in substance, and usually the site of dense calcification. In the past, attempts were made to restore function to such valves by debridement, commissurotomy or other reconstructive procedures, but experience has shown that these operations are ineffective in providing lasting benefit. Thus, when operative treatment becomes necessary in the adult with acquired aortic valve disease, it must be assumed that total replacement of the valve will be necessary.

The Starr-Edwards prosthesis has been most widely utilized for aortic valve replacement, and between February 1963 and September 1967 it was employed in 175 patients undergoing valve replacement at the National Heart Institute. The early and late results of operation in these patients are summarized in the present report.

The Patients

The 175 patients were 16 to 68 years of age (mean 47 years); 136 were men and 39 women. All were distinctly symptomatic; 36 were in functional Class II (New York Heart Association Criteria), 123 in Class III, and 16 in Class IV. The patients in Class II were all severely limited by episodic angina pectoris or syncope or both. On examination, the usual physical, roentgenographic and electrocardiographic findings associated with aortic valve disease were present. All patients were studied preoperatively by cardiac catheterization and selective angiography. Pure or predominant aortic stenosis was present in 76 patients, and pure or predominant aortic regurgitation in 59

patients. In 40 patients stenosis and regurgitation were considered of similar severity. Thirteen patients had defective aortic prostheses of other types, and four had aneurysms of the ascending aorta which necessitated resection or aneurysmorrhaphy. Excluded from present consideration are other patients in whom aortic valve replacement was accompanied by an operation on the mitral or the tricuspid valve or both.

The aortic valve was exposed during total cardiopulmonary bypass conducted during mild (30°C) general hypothermia. The left coronary artery was perfused. The diseased valve and any residual calcific deposits in the annulus and septum were resected, and a prosthesis of suitable size inserted. The valves were those available at the time, and they had silastic poppets and bare metal struts and orifices (Models 1000 or 1200). In virtually all patients anticoagulation with warfarin was instituted in the early postoperative period and maintained thereafter.

The Results

Immediate Mortality. Twenty-four patients (14 percent) died during the hospital admission at which valve replacement was performed. Nine patients died in the operating room, five as a result of technical problems related to placing the valve or closing the aorta; four other patients could never sustain an effective circulation after bypass, and one of them was found at necropsy to have severe and unrecognized mitral stenosis. Postoperatively, fatal hypotension and low output occurred in three patients, possibly because the prosthesis was too large for the aorta. Five patients died of uncontrollable ventricular arrhythmia, and three of renal failure. Cerebral hemorrhage, infected aortotomy, pulmonary consolidation, and endocarditis caused one death each.

Late Mortality. Thirty-eight of the original 175 patients (22 percent) have died at intervals of three months to five years after operation. In ten patients death was sudden and unexpected, and no anatomic cause was apparent at necropsy. Ten other patients have died as the result of degeneration of the silastic ball. The remaining 18 patients died of various causes, including left ventricular failure, arrhythmia, myocardial infarction, endocarditis and hepatitis.

Thromboembolism. Since 1965, all patients with Starr-Edwards valves have been given therapeutic doses of warfarin unless a specific contra-

Dr. Morrow is Chief, Clinic of Surgery, National Heart Institute, Bethesda, Maryland.

indication existed. Twenty-eight of the 113 surviving patients have had a total of 31 cerebral emboli with definite neurologic abnormalities. Twenty-five of the 28 patients recovered without detectable neurologic sequelae; in two patients mild residual abnormality persists, and in the other moderate weakness of the arm prevents employment. A number of other patients have described brief episodes of vertigo, paresthesia or aphasia, but none has ever had a neurologic abnormality on examination. Two patients who died suddenly and unexpectedly were found at necropsy to have coronary artery emboli.

Eight patients have experienced bleeding as the result of warfarin administration, and two of them with intracranial bleeding (intracerebral or subdural) died.

Symptomatic Improvement. The 113 surviving patients have been followed for periods of one to five years (average 34 months) and detailed reassessments have been made in all. Eighty of the 113 survivors (71 percent) are asymptomatic (Class I), while the remaining 32 experience symptoms only during unusual activity (Class II).

Hemodynamic Improvement. Postoperative cardiac catheterization has been performed in 100 patients at an average interval of seven months postoperatively. A systolic gradient across the prosthesis was usually evident, but the average value at peak systole was only 12 mm of mercury. The left ventricular end-diastolic pressure exceeded 15 mm of mercury in 66 patients preoperatively; it fell postoperatively in all but four of these, and the value was greater than 15 mm in only 15 patients postoperatively. The cardiac index was usually normal both before and after operation in patients with aortic stenosis. In two-thirds of those with aortic regurgitation it was abnormally low preoperatively, and normal in all but three postoperatively.

Some Conclusions Concerning Aortic Valve Replacement

The immediate risk of aortic valve replacement is 10 to 15 percent, and a significant number of survivors may be expected to die later of causes

directly or indirectly related to the operation or the prosthetic valve. Thus, at this time operation should only be recommended to distinctly symptomatic and severely incapacitated patients, those in whom the risk of early death without operation can reasonably be considered equal to or greater than that associated with valve replacement. In the child or adolescent, valve replacement is certainly to be avoided in all but extreme circumstances. The diagnosis of aortic stenosis or aortic regurgitation is readily apparent on clinical examinations, but information concerning the severity of the malformation can only be obtained by appropriate hemodynamic and angiographic studies. Such studies should be applied preoperatively in most patients, to provide assurance that symptoms are entirely or principally attributable to the defective valve and that improvement can be expected after valve replacement. When severe stenosis or regurgitation is proved to be present in a severely symptomatic patient, operation is always recommended. Certain preoperative findings, such as previous myocardial infarction, probably indicate an increased operative risk, but at this time none constitutes an absolute contraindication to operation.

Patients who survive operation derive gratifying symptomatic improvement, and in most of them this is accompanied by a return of the intracardiac pressures to normal or near-normal values.

These attitudes and conclusions concerning aortic valve replacement are based almost entirely on relatively early experiences with Starr-Edwards prostheses. Early mortality can certainly be reduced by more exact intraoperative and postoperative management, and almost two-thirds of the early deaths in this series could now be avoided. Also, valves used since September 1967 have metallic poppets, which should be indestructible, and fabric covering of the orifice and struts should eliminate or greatly reduce the incidence of systemic embolization. With these valves permanent anticoagulation therapy is considered unnecessary. When there is sound evidence that modifications of the operation and the prosthesis have reduced the risk of late death or disability, valve replacement can then be recommended to patients early in the course of their disease.

Attention Pediatricians!

Heinz Eichenwald, M.D., Professor of Pediatrics, University of Texas, Southwestern Medical School, will speak at the Pediatric Section meetings of the Annual Scientific Assembly, March 8 and 9. Plan to attend.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

ABRAHAM, HERMANN, Beverly Hills. Died 27 September 1969 in Los Angeles of myocardial infarction, aged 71. Graduate of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, 1925. Licensed in California in 1934. Doctor Abraham was a member of the Los Angeles County Medical Association.



ABRAHMS, EDWARD T., Los Angeles. Died 11 September 1969 in Los Angeles of heart disease, aged 62. Graduate of Tufts College Medical School, Boston, 1932. Licensed in California in 1938. Doctor Abrahms was a member of the Los Angeles County Medical Association.



BODLANDER, JEROME WILLIAM, Los Angeles. Died 13 September 1969 in Los Angeles of coronary artery occlusion, aged 61. Graduate of St. Louis University School of Medicine, 1933. Licensed in California in 1934. Doctor Bodlander was a member of the Los Angeles County Medical Association.



CANNON, ESPEY F., Redlands. Died 7 September 1969 in Redlands, aged 57. Graduate of Harvard Medical School, Boston, 1936. Licensed in California in 1945. Doctor Cannon was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



CHAPMAN, GEORGE ERIC, Santa Rosa. Died 11 February 1969 of pneumonia, aged 88. Graduate of Medical Faculty of Trinity University, Toronto, 1903. Licensed in California in 1917. Doctor Chapman was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.



CONRAD, CHESTER AMOS, Reseda. Died 16 September 1969 in Long Beach of ruptured abdominal aneurysm, aged 59. Graduate of Temple University School of Medicine, Philadelphia, 1934. Licensed in California in 1950. Doctor Conrad was an associate member of the Los Angeles County Medical Association.



FINESILVER, BENJAMIN, Hollywood, Florida. (Formerly of Los Angeles.) Died 15 September 1969 in Holly-

wood, Florida, of cancer, aged 70. Graduate of Long Island College of Medicine, New York, 1921. Licensed in California in 1942. Doctor Finesilver was a member of the Los Angeles County Medical Association.



HYDE, DEAN L., Fresno. Died 5 September 1969 in Provo, Utah, of injuries received in a plane crash, aged 51. Graduate of The George Washington University School of Medicine, Washington D.C., 1944. Licensed in California in 1946. Doctor Hyde was a member of the Fresno County Medical Society.



KIPEN, CHARLES SAMUEL, Los Angeles. Died 6 September 1969 in Los Angeles of cancer, aged 55. Graduate of University of Wisconsin Medical School, Madison, 1938. Licensed in California in 1946. Doctor Kipen was a member of the Los Angeles County Medical Association.



KRANZDORF, CHARLES DAVID, Encino. Died 2 September 1969 at Valley Receiving Hospital, Los Angeles County, of acute myocardial infarction-arteriosclerotic heart disease, aged 41. Graduate of the College of Physicians and Surgeons, Los Angeles, 1954. Licensed in California in 1955. M.D. degree from California College of Medicine, 1962. Doctor Kranzdorf was a member of the Los Angeles County Medical Association.



MAGID, HENRY JOSEPH, Burbank. Died 1 September 1969 at Lake Louise, Canada, of heart disease, aged 59. Graduate of the University of Colorado School of Medicine, Denver, 1936. Licensed in California in 1937. Doctor Magid was a member of the Los Angeles County Medical Association.



POWERS, ALLAN RAYMOND, Tracy. Died 16 September 1969 in Tracy, aged 88. Graduate of Cooper Medical College, San Francisco, 1912. Licensed in California in 1912. Doctor Powers was a retired member of the San Joaquin County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



REICHERT, FREDERICK LEET, Honolulu. Died 23 September 1969 in Bethesda, Maryland, of pneumonia, aged 75. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1920. Licensed in California in 1926. Doctor Reichert was a member of the San Francisco Medical Society.



TUTUNJIAN, KHACHER H., Los Angeles. Died 4 September 1969 in Los Angeles of gastrointestinal hemorrhage, aged 72. Graduate of Rush Medical College, Chicago, 1932. Licensed in California in 1941. Doctor Tutunjian was a member of the Los Angeles County Medical Association.

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

Mumps Virus Vaccine

MUMPS IS NOT the harmless childhood disease we once believed it to be. At the very least, it is a painful and inconvenient disease which generally requires seven to ten days' absence from school or normal workday routine.

In approximately 10 percent of mumps cases, there are symptoms of central nervous system involvement.¹ Since a decidedly increased spinal fluid lymphocyte count is a frequent finding in mumps without apparent signs or symptoms of involvement of the central nervous system, the actual incidence of meningo-encephalitis due to mumps virus may be much higher than reported. The CNS involvement usually subsides within seven days without observable sequelae, but any meningo-encephalitic inflammation carries with it the risk of CNS damage which may be expressed in behavioral and personality changes or in learning disabilities. It should also be noted that approximately 50 deaths are attributed to mumps in the United States each year, the majority of which result from mumps meningo-encephalitis.²

The most dramatic complication of mumps, and perhaps the most overemphasized, is orchitis, which occurs in an estimated 20 to 25 percent of post-pubertal males having the disease.³ About 30 percent of mumps orchitis cases result in testicular atrophy, which in turn may result in lowered sperm count. Some impairment of fertility is found in an estimated 15 percent of patients who have had mumps orchitis, but absolute sterility as a result of this complication is rare.³ Perhaps more important than physiological changes, however, is the psychological damage to the victims; in some cases, such fears can be the cause of impotence.³

Pancreatitis as a result of mumps appears to vary in frequency from epidemic to epidemic, occurring in from 2 to 5 percent of cases in different studies.¹

It seems to occur more frequently in women. Since the presenting symptoms are usually abdominal pain and vomiting, which could also be indicative of oophoritis, a serum amylase determination is often helpful in differential diagnosis. Recent investigations have suggested a connection between pancreatic involvement during mumps and subsequent diabetes.¹ Twenty cases of diabetes following mumps pancreatitis have been described. While the causal relationship has not been shown, it will be important to learn whether the beta cells are significantly involved in mumps pancreatitis.²

Other mumps complications, including temporary or permanent deafness, optic nerve involvement, thyroiditis and mastitis, are rare.¹ An association has been made between maternal mumps during pregnancy and the rare condition of cardiac fibroelastosis of the newborn,² but much further investigation will be required to establish a causal relationship.

Mumps-preventing vaccines have been available since 1950, but earlier forms, consisting of killed or inactivated mumps virus, provided only temporary protection. They were not recommended for children because of the possibility of their simply postponing the disease until adult life when the complications might be more serious.³ The development in 1966 of a safe and effective live attenuated mumps virus vaccine has finally afforded a preventive measure capable of bringing about the control of this disease.

Mumps Virus Vaccine, Live, Attenuated, MSD (Mumpsavax®) causes the formation of neutralizing antibodies and thus protects against the disease in more than 95 percent of susceptible persons, according to recent studies. Trials to date have not shown any significant side effects from the vaccine; the incidence of fever and soreness at the site of injection is minimal.⁴

A decision of the Public Health Service Advisory Committee on Immunization Practice in October 1968 broadened the recommended use of the vaccine to include susceptible children aged one year and over as well as the susceptible adolescents and adults who had previously been the priority group. In order to facilitate the further analysis of the attenuated live virus mumps vaccine, it should be

given at least a month apart from any previous or subsequent injection.⁴

Lack of knowledge of what is available, coupled with misconceptions about the safety of mumps vaccine and the wisdom of prevention, keep patients from requesting the vaccine although they might benefit from it. Physicians can go a long way toward reducing California's high incidence of mumps infection by making patients aware of the

possibility of preventing this inconvenient and potentially serious disease safely and effectively.

REFERENCES

1. Karzon, David T.: Rationale for mumps vaccine usage, *In* Proceedings of the 5th Annual Immunization Conference, 1968.
2. Stokes, Joseph: Prevention and treatment of mumps, *Sandoz Panorama*, 6:10, Dec. 1968.
3. Stokes, Joseph: Mumps and manhood, Part 3 of Press Information Series.
4. Stokes, Joseph: Mumps vaccine (A description of the Merck, Sharp, & Dohme mumps virus vaccine, including clinical trials), 1967.

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Attention Obstetricians and Gynecologists

Robert W. Kistner, M.D., Assistant Clinical Professor of Obstetrics and Gynecology, Harvard Medical School, will speak at the Obstetrics and Gynecology Section meeting of the Annual Scientific Assembly, March 9. Mark your calendar!

application for **HOTEL ACCOMMODATIONS**

NINETY-NINTH *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION • MARCH 7-11, 1970

SAN FRANCISCO HILTON HOTEL, SAN FRANCISCO

**HOUSE OF DELEGATES OPENING SESSION, HILTON HOTEL, SATURDAY EVENING, MARCH 7;
SCIENTIFIC SESSIONS, HILTON HOTEL, BEGIN SATURDAY NOON, MARCH 7**

1. Fill in the form below *completely* for room accommodations at the CMA's 1970 Annual Session. There are only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
 2. Your reservation request should include the definite date and hour of your arrival and departure.
 3. All reservations must be made through the CMA Housing Bureau, Suite 260, Fox Plaza, San Francisco, California 94102, by February 6, 1970.
 4. **CANCELLATIONS:** Please notify CMA Housing Bureau, Suite 260, Fox Plaza, San Francisco 94102 of all cancellations up to 15 days before Annual Session. Within last 15 days, make cancellations directly with hotel.
- CHANGES:** All other changes to be made directly with hotel at all times. Rooms will not be held after 6 P.M. unless a later arrival time has been requested. Failure to notify the hotel of any change in your arrival time may result in cancellation of your reservation.

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Please reserve the following accommodations for the CMA's 1970 Annual Session in San Francisco, March 7-11.

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Your Name: Officer? Delegate? Alternate? Speaker?

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1970 ANNUAL SCIENTIFIC ASSEMBLY

of the California Medical Association

San Francisco, March 7-11

Topics of the three general meetings:

What is family practice?

Manpower — new aids to the physician

Systems of delivery for health care services

Renowned Speakers Are:

LYNN P. CARMICHAEL, M.D.

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Executive Director
National Committee Against Mental Illness
Washington, D. C.

HENRY K. SILVER, M.D.

Professor of Pediatrics
University of Colorado Medical Center

EUGENE A. STEAD, JR., M.D.

Department of Medicine
Duke University Medical Center

L. HENRY GARLAND MEMORIAL LECTURE — MARCH 8

Guest Speaker: Melvin P. Judkins, M.D., Professor of Radiology and Director, Cardiovascular Laboratories, University of Oregon Medical School.

Title: "A Breakthrough in the Battle with Coronary Artery Obstructive Disease."

CONTINUING EDUCATION

ACTIVITIES

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

- CMA:** California Medical Association
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University
Contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University
Contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5940.
- UCD:** University of California, Davis
Contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0333.
- UCI:** University of California — California College of Medicine, Irvine
Contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA:** University of California, Los Angeles
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
- UCSD:** University of California, San Diego
Contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
- UCSF:** University of California, San Francisco
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

CANCER

December 7 — **California Tumor Tissue Registry — Semi-Annual Cancer Conference.** Beverly Hilton Hotel, Beverly Hills. Sunday 9:00-5:30. Lymphomas and Hodgkin's Disease. Contact: W. K. Bullock, M.D., Exec. Dir., Los Angeles County Hospital, 1200 N. State St., Los Angeles 90033.

December 13 — **Radiotherapy Symposium — Lymphomas & Hodgkin's Disease.** Southern California Permanente Medical Group at Ambassador Hotel, Los Angeles. Saturday, 8:30 a.m.-3:30 p.m. Pathological classifications, medical aspects, and chemotherapy. Contact: Shirley Gach, Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

January 5-10—**Pacific Cancer Conference.** American Cancer Society, Hawaii Division, Inc. at Hilton Hawaiian Village Hotel, Honolulu. Monday-Saturday. Reservations accepted on a first-come basis. \$479.31. Contact: H. Robert Bryman, Professional Consultants, Inc., 3194 Lawson Blvd., Oceanside, New York 11572.

February 21-25—**Current Concepts in Cancer Chemotherapy.** UCLA at El Mirador Hilton Hotel, Palm Springs. Saturday-Wednesday.

MEDICINE

December 1-12 — **Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly through May, 1970. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitors, placement of pacing catheters, new aspects in diagnosis and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P. H., Administrative Associate, CRMP, Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.

December 2-5—**Reticuloendothelial Society—6th Annual Meeting.** Jack Tar Hotel, San Francisco. Tuesday-Friday. Tuesday 7:30 p.m., Keynote Address. Wednesday-Thursday, seventy-six papers presented. Friday, Symposium on Recent Aspects of RES research. Contact: Ernest L. Dobson, Ph.D., General Chairman, Donner Laboratory, University of California, Berkeley 94720.

December 4-6—**Cardiovascular Therapeutics.** American College of Cardiology in cooperation with UCSD, Scripps Clinic and Research Foundation, San Diego County Heart Assoc., and California Heart Assoc. at UCSD. Thursday-Saturday. Thursday: Treatment of Coronary Artery Disease. Friday: Cardiac Pharmacology. Saturday: Surgical Treatment of Heart Disease. \$50 for ACC members, \$85 for nonmembers. Contact Eugene Braunwald, M.D., Professor and Chairman, Dept. of Medicine, UCSD.

December 12-14—**Coronary Artery Disease and Cardiovascular Therapeutics.** American College of Cardiology in cooperation with University of Hawaii School of Medicine at Ilikai Hotel, Honolulu. Friday-Sunday. Natural history and anatomy of coronary artery disease, cardiac conduction system, sudden death, newer anti-arrhythmic drugs and adrenal blocking agents, current status of implantable pacemaker, revascularization of myocardium and coronary care monitoring. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

December 16—Recent Developments in Diagnosis of Contact Dermatitis. UCSF at Hilton Hotel, San Francisco. Tuesday. Patch Testing Techniques, Cosmetic Allergy, Ointment Base Allergy.

January 13-14—The American College of Cardiology—Annual Conference on Clinical Cardiology: New Developments in Diagnosis, Evaluation and Medical and Surgical Aspects of Therapy. American College of Cardiology in cooperation with UCD and Sacramento Medical Center at Sacramento Medical Center, Sacramento. Tuesday-Wednesday. Designed for generalist, internist and cardiologist. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

January 14—Seminar on Respiratory Diseases. Tuberculosis and Respiratory Disease Association of Contra Costa at Holiday Inn, Concord. Wednesday 9-5:00. Didactic sessions and group seminars will cover allergic aspects of respiratory disease in children and adults, infectious respiratory disorders and the spectrum of chronic obstructive lung disease, film on spirometry. Contact: Mitchell Tarkoff, M.D., Chairman, Medical Education Committee, TB and Respiratory Disease Assoc. of Contra Costa, 105 Astrid Drive, Pleasant Hill 94523. (415) 935-0472.

January 16-17—Modern Trends in Epilepsy. UCSF. Friday-Saturday. Critical Analysis of Team Approach, Epilepsy in Childhood, Epilepsy and Personality.

January 16-18—Total Rehabilitation—A Road to Work for "Unemployable" Cardiac Patients. Ben R. Meyer Rehabilitation Center of Cedars-Sinai Medical Center, Cedars of Lebanon Hospital Division at Sheraton-Universal Hotel, Los Angeles. Thursday-Sunday. Contact: John H. Aldes, M.D., Director, Ben R. Meyer Rehabilitation Center, Cedars of Lebanon Hospital Division, 4833 Fountain Ave., Los Angeles 90029.

January 17—Workshop in Advanced Arrhythmias. PMC. Saturday.

January 21—14th Annual Midwinter Symposium on Cardiovascular Research. Los Angeles County Heart Association at the Hilton Hotel, Los Angeles. Wednesday. Contact: Joe Kennelley, Director, Public Information, LACHA, 2405 West 8th St., Los Angeles 90057. (213) 385-4231.

February 2-3—Symposium of Arrhythmias. American College of Cardiology in cooperation with UCI at Newporter Inn, Newport Beach. Sunday-Tuesday. Latest anatomical, pharmacological, and physiological bases for disturbances of cardiac rhythm related to specific disease entities and situations. Workshops will demonstrate clinical application of basic concepts. Contact: UCI.

February 6—Stroke Symposium. CRMP, Area VII at Hotel Del Coronado, Coronado. Friday. \$10. Contact: Michael Shimkin, M.D., Director, CRMP, Area VII, 7816 Ivanhoe, La Jolla 92037. (714) 459-3739.

February 12-13—Symposium on Hematology. UCSF. Thursday-Friday.

February 13-14—American College of Physicians — Northern California-Nevada Regional Meeting. Mark Thomas Inn, Monterey. Friday-Saturday. Contact: John R. Gamble, M.D., Governor, No. Calif. and Nevada Region, ACP, 655 Sutter Street, San Francisco 94102. (415) 673-4080.

February 17-18—American College of Physicians — Hawaii Regional Meeting. Pacific Club, Honolulu. Tuesday-Wednesday. Tuesday and Wednesday a.m., Scientific Sessions. Tuesday p.m., Lecture in connection with The American College of Surgeons, "What's Left in Thyroid Disease for the Surgeon?" Contact: Morton E. Berk, M.D., Governor, Hawaii Region, ACP, 1133 Punchbowl Street, Honolulu.

February 20-21—American College of Physicians — Southern California Regional Meeting. Coronado. Friday-Saturday. Contact: Eugene Braunwald, M.D., Chairman of Scientific Program, UCSD.

February 21—Advances in Cardiology. USC at Huntington-Sheraton Hotel, Pasadena. Saturday.

February 28-March 1—Your Patient with Renal Disease. UCSF at Franklin Hospital, San Francisco. Saturday-Sunday.

March 5-6—Endocrine Disease. USC. Thursday-Friday.

March 5-6—Dialogues in Dermatology. UCSF at Sir Francis Drake Hotel, San Francisco. Thursday-Friday.

March 14—Auscultation of the Heart. PMC. Saturday.

March 26—Obesity. USC. Thursday.

Continuously—Basic Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

Grand Rounds—Medicine

Tuesdays

9-10:30 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Wednesdays

Grand Rounds in Internal Medicine. 10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.
11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

Grand Rounds in Internal Medicine. 12:30-1:30 p.m., University Hospital, UCSD.

Grand Rounds in Internal Medicine. 1:30-3:00 p.m., Fresno General Hospital.

Thursdays

10:30-12:00 noon, Room C3-105, UCLA Medical Center. UCLA.

Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundations.

2-3:00 p.m., Classroom, Third Floor, Fresno General Hospital, Fresno. CRMP Area IV.

Rheumatology Grand Rounds. 11:30 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

OBSTETRICS AND GYNECOLOGY

December 6—Obstetrics and Gynecology. PMC. Saturday. 8:30-4:30. New clinical concepts and problems for the family physician and the gynecological surgeon.

February 20-21—Family Planning and Therapeutic Abortion. UCSF. Friday-Saturday.

PEDIATRICS

December 6-7 — Second Annual Childrens Hospital Medical Center Symposium. UCI in cooperation with Long Beach Pediatric Society and the Childrens Psychiatric Clinic at Memorial Hospital of Long Beach. Saturday-Sunday. Adolescence: Normal Development, Behavioral and Psychiatric Disorders, Drug Abuse. Contact: Harry W. Orme, M.D., Medical Director, Dept. of Pediatrics, Memorial Hospital of Long Beach, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-2311.

February 7—Pediatric Urology. UCSF at Childrens Hospital, San Francisco. Saturday.

February 9-20—Mental Retardation. UCLA in cooperation with Pacific State Hospital, Pomona, at UCLA Neuropsychiatric Institute. Two weeks. For physicians and allied professionals. Causation, symptomatology, care, treatment and management, diagnostic techniques suitable for office practice, parental reactions and intra-family psychopathology, and recent research findings. Contact: UCLA.

March 7 — Pediatric Hematology. UCSF at Childrens Hospital and Adult Medical Center, San Francisco. Saturday.

March 13-14—Child Neurology: Recent Advances. UCSF. Friday-Saturday.

March 23-26—Clinical Evaluation of Children with Learning Disorders. UCSF. Monday-Thursday.

March 27-28—Pulmonary Disease in Neonates. UCI, CRMP Area VIII in cooperation with the National Cystic Fibrosis Research Foundation at Childrens Hospital of Orange County. Friday-Saturday. Registration by March 1 is necessary. Contact: William F. Taylor, M.D., Pediatric Pulmonary Demonstration Center, UCI.

Grand Rounds—Pediatrics

Tuesdays

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Conference Room, Sixth Floor, Harbor General Hospital, Torrance. CRMP Area IV.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and the Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Stanford University Medical Center, Palo Alto.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

PSYCHIATRY

December 6-7 — Group Therapy and Personality Changes. UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday. Various aspects of group psychotherapy; the marathon group, couples and family groups, psychoanalytic and group psychotherapy. \$15.

December 13—Psychiatric Perspectives in Medicine. UCSF at Stockton State Hospital, Stockton. Saturday. Unresolved conflicts of early childhood, problems inherent in early diagnosis and treatment of emotional disorders, administration of therapy.

January 7—Group Methods. UCSF at V.A. Hospital, San Francisco. Wednesdays 11:30 a.m.-1:00 p.m. through March 11. For physicians and para-professionals in the mental health field. Various aspects of group psychotherapy; personal experience in group process, role playing, group treatment and the generation gap, couples, family, adolescent and marathon groups and color marathon racial confrontation. \$25 full program, \$2 individual lectures.

March 14-15—Current Theories in Psychiatry. UCSF at Napa State Hospital, Napa. Saturday-Sunday.

March 14-15—The Troubled Adolescent in the Modern Family. UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

March 20-21 — Suicide Prevention and Advanced Workshop. UCSF. Friday-Saturday.

March 23-26—American Orthopsychiatric Association. Mark Hopkins and Fairmont Hotels, San Francisco. Monday-Thursday. Contact: Marion F. Langer, Ph.D., 1790 Broadway, New York 10019.

RADIOLOGY—PATHOLOGY

December 5-7 — California Society of Pathologists — Annual Winter Meeting. Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. Presented in conjunction with College of American Pathologists, a Program on Infectious Hospital Diseases and a Seminar on Lymphomas and Hodgkin's Disease presented by the California Tumor Tissue Registry. Contact: L. Miles Snyder, Exec. Sec., California Society of Pathologists, 1831 I St., Sacramento 95814. (916) 443-6744.

January 31-Feb. 1—Los Angeles Radiological Society—22nd Annual Midwinter Radiological Conference. International Hotel, Los Angeles. Saturday-Sunday. Diagnosis, therapy, and nuclear medicine. \$30. Contact: Arthur F. Schanche, M.D., 8618 So. Sepulveda, Suite 100, Los Angeles 90045.

March 1-6—**American Radium Society.** Hotel del Coronado, Coronado. Sunday-Friday. Contact: John V. Blady, M.D., Secretary, ARS, 2201 Benjamin Franklin Parkway, Philadelphia 19130.

March 3-7—**Diagnostic Radiology.** UCSF. Tuesday-Saturday.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

SURGERY—includes Anesthesiology

December 4-6—**Diagnosis and Management of Uveitis—Annual Proctor Foundation Program.** UCSF. Thursday-Saturday. \$125.

December 12-14 — **Office Procedures in Orthopedics.** UCLA. Friday-Sunday. Geared to the physician in general practice.

December 12-14—**Fluid and Electrolyte Balance.** USC at El Mirador Hotel, Palm Springs. Friday-Sunday. Water and electrolyte balance and its application to patients. Dehydration and hypovolemia, acid-base balance, disturbances in osmolarity, and potassium. \$75.

January 10-11—**Psychiatric Implications of Newer Surgical Horizons.** UCSF at Sutter Memorial Hospital, Sacramento. Saturday-Sunday.

January 12-16—**Otologic Surgery.** Los Angeles Foundation of Otolaryngology and USC in cooperation with St. Vincent's Hospital at St. Vincent's Hospital, Los Angeles. Monday-Friday. One day will be devoted to otosclerosis surgery, three days to surgery of chronic ear disease. One day devoted to inner ear problems, glomus tumors, and facial nerve paralysis. Contact: Glenn Snyder, Managing Director, Los Angeles Foundation of Otolaryngology, 2130 W. Third St., Los Angeles 90057. \$300.

January 17-18—**Cadaver Course.** Research Study Club of Los Angeles at USC. Saturday, 2-5 p.m.; Sunday, 9 a.m.-3 p.m. Surgical Anatomy of the Orbit and Adnexa, Individual Dissection. Limited to 20 applicants attending the Thirty-Ninth Annual Mid-Winter Convention in Ophthalmology and Otolaryngology. \$50. Contact: Burns C. Steele, M.D., Secretary, Research Study Club of Los Angeles, 1141 W. Olive Avenue, Burbank 91506. (213) 846-3614.

January 19-23—**Research Study Club of Los Angeles—39th Annual Mid-Winter Convention in Ophthalmology and Otolaryngology.** Statler Hilton Hotel, Los Angeles. Monday-Friday. Simultaneous lectures in Otolaryngology and Ophthalmology. \$100. Contact: Burns C. Steele, M.D., Secretary, Research Study Club of Los Angeles, 1411 W. Olive Ave., Burbank 91506. (213) 846-3614.

January 23-25—**Pediatric Anesthesiology—8th Annual Clinical Conference.** Childrens Hospital of Los Angeles at Childrens Hospital. Friday-Sunday. Pre-anesthetic evaluation, methods of induction, choice of agent, pharmacology, iatrogenic diseases, and postoperative care. \$75. Contact: Wayne Herbert, M.D., Division of Anesthesiology, Childrens Hospital of Los Angeles, P.O. Box 54700, Los Angeles 90054.

January 26-30—**Techniques in Nasal Surgery.** UCLA. Monday-Friday.

February 1-4 — **Surgical Anatomy.** LLU. Sunday-Wednesday. \$150.

February 7 — **Surgical Emergencies.** PMC. Saturday 8-4:30. Morning session: Monitoring and Management of Shock. Afternoon: Selected and control problems, workshop including case studies and exercises involving blood and gas data, venous pressures.

February 25-March 1—**Controversial Areas in Surgery.** UCLA at El Mirador Hotel, Palm Springs. Wednesday-Saturday.

March 14-15—**Techniques of Surgery of the Foot.** UCLA. Saturday-Sunday.

March 19-21—**Medical Ophthalmology.** UCSF. Thursday-Saturday.

March 25-28—**Neurosurgical Society of America.** Ojai Valley Hotel, Ojai Valley. Wednesday-Saturday. Contact: William F. Collins, M.D., Secretary, NSA, 789 Howard Avenue, New Haven, Conn. 06510.

Grand Rounds—Surgery

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

Fridays

12:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

9:30 a.m., Neuroradiology; 10:15, Neurology; 11:15, Neurosurgery. Neurology Conference Building 7, V.A. Hospital, Palo Alto. STAN.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

OF INTEREST TO ALL PHYSICIANS

December 3 — **Postgraduate Assembly — Virology for the Practicing Physician — St. Luke's Hospital of Pasadena.** At the Huntington-Sheraton Hotel, Pasadena. Wednesday, 9-5:00. Historical and comprehensive discussions; slow viruses, the clinician and the viral diagnostic laboratory, etiology of hepatitis, management of virus diseases, prevention of viral disease, virus and cancer. Contact: W. K. Bullock, M.D., Chairman, 1969 Postgraduate Assembly, 2632 E. Washington Blvd., Pasadena 91107.

December 5-6—**Nasal Obstruction.** STAN. Friday-Saturday. A 2-day Symposium on Advances in Diagnosis and Treatment. Of special interest to allergists and otolaryngologists. \$50. Contact: Richard L. Goode, M.D., Div. of Otolaryngology, STAN.

January 2-4—Medicine and Law. The American College of Physicians and USC Postgraduate Psychiatry Dept. at USC. Friday-Sunday. Of special interest to physicians in clinical hospital administrative and teaching roles. Broad overview of significant interface between medicine and law, both theoretical and practical. Medical malpractice will not be a major consideration. \$60 for ACC members, \$100 for nonmembers. Contact: Donald N. Naftuline, M.D., Director, Postgraduate Psychiatry, USC.

January 8-9—Drug Therapy. UCSF. Thursday-Friday. Drugs and liver disease, oral contraceptives, treatment and prevention of congestive failure.

January 15-16—New and Old Antibiotics. USC. Thursday-Friday.

January 21-April 29—Clinical Psychiatry for Non-Psychiatrists: A Course in Medical Psychotherapy. UCSF. Wednesdays 1-5:00. Open to physicians and paramedical specialists, enrollment limited to 14. Weekly interviews with psychiatric patients, supported by individual hours of faculty consultation and joint treatment reviews of all patients and seminars. Seminars will cover diagnosis and management of psychiatric emergencies, psychiatric illness in children, testing, and community psychiatry. \$25.

January 24 — West Coast Postgraduate Course, San Luis Obispo. CMA and UCI at Sierra Vista Hospital and San Luis Obispo General Hospital. Saturday. Clinical endocrinology. Contact: CMA.

January 25 — Office Emergencies, A Symposium for Medical Assistants. UCSF. Sunday.

January 29-30—Southern Counties Regional Postgraduate Institute. CMA, STAN, and Southern Counties Medical Societies at El Mirador Hotel, Palm Springs. Thursday-Friday. Thursday a.m.: Acute Injuries of Hand and Face, Acute Cardiac Emergencies and Their Management. Thursday afternoon: The Comatose Patient, Acute Urological Problems. Friday a.m.: Acute Emergencies in the Infant and Child, Shock, Cranial and Spinal Cord Injuries, Acute Pulmonary Problems. Friday afternoon: Symposium on the Multiple Injured Patient.

January 30-Feb. 1 — Financial, Tax, and Investment Planning. UCLA. Friday-Sunday.

January 31-February 1 — Eighth Scientific Seminar Program. Memorial Hospital of Southern California, Memorial Hospital of Gardena, and Brotman Foundation of California at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Coma, Adolescent Medicine and Chaos, The Patient with Disordered Blood Coagulation, Arthritis—1970. \$15. Contact: David M. Brotman, M.D., Secretary, Seminar Committee, Memorial Hospital of Southern California, 3828 Hughes Ave., Culver City 90230. (213) 834-3111.

February 7—Suicide. UCSF. Saturday.

February 7-8—Drug Abuse. UCSF at Mendocino State Hospital, Talmadge. Saturday-Sunday.

February 9, 10, 11-March 2, 3, 4—Annual Postgraduate Circuit Courses—Spring Session. CMA and STAN at Mt. Shasta Community Hospital; Enloe Memorial Hospital, Chico; and Auburn Faith Hospital, Auburn.

Radiotherapy and Cancer Management, Depression — Disease and Symptom, Pathology — Past, Present and Future, and Injuries of the Hand and Face. \$30. Contact: CMA.

February 9-13 — Course for Physicians in General Practice. UCSF at Mt. Zion Hospital and Medical Center, San Francisco. Monday-Friday. Geriatrics, Allergy, Topics in Endocrinology, Surgical Methods 1970, Cardiovascular Topics, Pediatrics.

February 11-12—Critical Care Medicine and Circulatory Shock. USC. Wednesday-Thursday.

February 14—Cardiac Emergencies. PMC. Saturday. Therapy of intractable heart failure, modern concepts of shock, and emergencies arising in the infant.

February 15—Annual Symposium—Hollywood Community Hospital at Sheraton-Universal Hotel, Hollywood. Sunday. Contraceptive and Sexual Problems. Contact: Viola Kindstrand, Symposium Secretary, Hollywood Community Hospital, 6245 de Longpre Avenue, Hollywood 90028. (213) 462-2271.

February 15-19—Loma Linda University School of Medicine, Alumni Association—Postgraduate Convention. Ambassador Hotel, Los Angeles, and LLU. Sunday-Thursday. Sunday-Monday: Refresher course, LLU. Tuesday-Thursday: Scientific Assembly, Ambassador Hotel. Contact: Samuel H. Fritz, M.D., General Chairman, Alumni Postgraduate Convention for 1970, LLU.

February 26-April 30—Teaching Clinics in Psychiatry. UCLA. Thursdays.

February 27-28—The Physician and Athletics. UCSF. Friday-Saturday.

February 28—Problems in Social Change Reflected in Medical Practice. UCSF at Herrick Memorial Hospital, Oakland. Saturday.

March 7-11—California Medical Association—Annual Scientific Assembly. Hilton Hotel, San Francisco. Saturday-Wednesday. General Sessions: Saturday p.m.: Family Practice. Sunday p.m.: Manpower. Monday p.m.: Systems of Delivery. Tuesday p.m.: Birth Defects. Guest Speakers for General Sessions include: Lynn P. Carmichael, M.D., University of Miami School of Medicine; Mike Gorman, National Committee Against Mental Illness; Jerome Pollack, Associate Dean for Medical Care Planning, Harvard Medical School; Henry K. Silver, M.D., Professor of Pediatrics, University of Colorado Medical Center; Eugene A. Stead, Jr., M.D., Duke University Medical Center. Assembly includes Special Conferences, Section Meetings, and medical motion picture symposia daily. More complete program listing in January pre-convention issue.

March 19-20 — Postgraduate Seminar and Clifford Sweet Memorial Lecture. Childrens Hospital of Oakland. Thursday-Friday. Sex Education for Physicians. Contact: Inetta Cartney, Childrens Hospital of Oakland, 51st and Grove Streets, Oakland 94609. (415) 654-5600.

March 25-26 — Los Angeles County Heart Association and Los Angeles Academy of General Practice—Seventh Annual Spring Symposium for Physicians Practicing General Medicine. Wednesday-Thursday. Contact: Joe Kennelly, Director, Public Information,

LACHA, 2405 W. Eighth Street, Los Angeles 90057. (213) 385-4231.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

TELEVISION

Southern California's Medical Television Network. UCLA. Weekly broadcasts, Tuesdays 8:30 a.m. Contact: UCLA Medical Television Network.

December 2—**Aggressive Management of the Stroke Patient.** Three part series. Part I: Differential Diagnosis and Early Medical Management. UCI, California College of Medicine.

December 9—**Aggressive Management of the Stroke Patient.** Part II: Early Post-Acute Care. UCI, California College of Medicine.

December 16—**Aggressive Management of the Stroke Patient.** Part III: Rehabilitation and Discharge Planning. UCI, California College of Medicine.

December 23—**Tumors of the Head and Neck, Part I.** Carcinoma of the Lip, Oral Tongue and Floor of the Mouth. Washington-Alaska Regional Medical Programs.

THERAPY FOR DIVERTICULAR DISEASE

"Though completely binding rules cannot be made for surgery in all patients with diverticular disease, we have found it wise to recommend surgery for: (1) all patients suffering more than one attack, with definite evidence of abdominal sepsis from diverticular disease; (2) patients with urinary bladder irritability, such as dysuria, microscopic hematuria, or suprapubic pain, not ascribable to intrinsic urinary system disease; (3) patients in whom there is the most remote possibility of cancer lurking in the benign shadow of diverticulitis; and (4) very selected patients with diverticular disease who develop colonic invalidism from chronic involvement of the sigmoid. Here is where we can commit errors in judgment. But here also is where thorough study of the patient and his reactions to diverticular disease may pay handsome dividends in easing his life as well as preventing serious complications in the future."

—A. F. CASTRO, M.D., Washington, D.C.

Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 1, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

periodic blood counts before and during therapy. Any unexpected, significant change in the total white count, relative differential, or appearance of abnormal forms should be regarded as a signal for immediate cessation of therapy and institution of appropriate countermeasures. Thrombocytopenia, purpura and aplastic anemia must be considered possible side effects of therapy with Butazolidin, brand of phenylbutazone.

Surgery: Prolonged use of prednisone may cause a potentially critical degree of adrenal insufficiency which may persist after cessation of prednisone therapy. If a patient is subjected to significant surgery or trauma, either during or after therapy or within one year of cessation of therapy, it is advisable to administer additional steroid and/or ACTH for support of the stress. Delayed wound healing may also occur in patients on prednisone therapy.

Infection: High or prolonged doses of steroids may interfere with the usual immune response against bacterial and viral infections and may promote their dissemination. In patients on steroid treatment should not be given prophylactic antibiotics unless appropriate antibiotic therapy is instituted at the same time. Systemic and localized infection complicating hormone therapy have been observed including fulminating pneumonia, sinusitis, moniliasis and aspergillosis. When a recurrent infection develops, antibiotic therapy must be initiated immediately. Every patient who is to receive steroids for any length of time should be carefully examined, including chest x-ray, to rule out presence of pulmonary or extrapulmonary tuberculosis.

Imbalance: Gluco-corticoids, in high dosage, may cause manifestations of Cushing's syndrome, such as moon face, abnormal fat deposits, mental depression, muscle weakness and atrophy, striae, acne, ecchymoses, hirsutism, menstrual disturbances, edema, osteoporosis, spontaneous fractures, and hypertension. Suppressing adrenocortical function, as in prednisone therapy may cause some atrophy of the adrenal glands. Therefore, when Sterazolidin is to be discontinued, the dosage should be tapered off gradually.

In addition, it may be advisable to stimulate the adrenal glands with ACTH. Prednisone induces a prompt decrease in the urinary 17-ketosteroids. Pretreatment levels are usually regained within 7 to 14 days after cessation of therapy. Under conditions of long-term administration, a small percentage of patients on phenylbutazone may develop varying degrees of reversible thyroid hyperplasia.

Allergic Response: Development of drug rash should alert the physician to promptly discontinue the drug. The presence of prednisone in Sterazolidin may reduce the degree of allergic response; nevertheless, the same cautious attitude must be preserved with Sterazolidin as with Butazolidin, brand of phenylbutazone, if allergic manifestations occur. Other adverse reactions that have been observed with glucocorticoid therapy include: excessive appetite and weight gain, hyperhidrosis, pigmentation, dry, scaly skin, thinning scalp hair, tachycardia, thrombophlebitis, headache, neuropathy (including paresthesias and neuritis), diffuse vasculitis similar to periarteritis nodosa, subcapsular cataracts, impaired renal function, lupus erythematosus-like changes, convulsions, insomnia, abdominal distention, aseptic necrosis of the femoral head, acute pancreatitis and ulcerative esophagitis.

Miscellaneous: Stomatitis and, rarely, salivary gland enlargement occasionally require the interruption of treatment with Butazolidin, brand of phenylbutazone. Adoption of a lower dosage schedule and the institution of strict oral hygiene sometimes prevent recurrence of lesions. The infrequent occurrence of such subjective sensations as vertigo or languor during therapy with Butazolidin, brand of phenylbutazone, is seldom a serious or significant complication. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hepatitis and jaundice, hypersensitivity angitis, pericarditis and several cases of anuria and hematuria. Patients should be carefully evaluated before treatment is started and those receiving Sterazolidin must remain under close medical supervision to guard against undesirable reactions such as

those described. They should be instructed to report immediately the occurrence of fever, sore throat, lesions in the mouth, or black or tarry stools. It is recommended that periodic examinations of the patient include:

1. Verbal and physical examination, including blood pressure and appraisal of the cardiovascular, digestive and skeletal systems, for indications of toxic reaction.
2. Complete blood count (at weekly intervals during the first month), urinalysis, x-ray and electrolyte studies, as indicated.
3. Check of patient's weight to detect significant water retention.

Dosage Dosage should be individualized. The following general rules should be observed:

In acute therapy, dosage should not exceed 12 capsules on the first day and 6 to 8 capsules on succeeding days. Treatment for more than 7 days is rarely necessary. When therapy extends beyond one week, dosage should not exceed 6 capsules a day.

In chronic therapy, dosage should not exceed 6 capsules a day and should be tapered off gradually to establish the minimum maintenance level at which the patient still feels reasonably comfortable. A trial period of one week of therapy is considered adequate to determine the therapeutic effect of the drug. In the absence of a favorable response, therapy should be discontinued.

When switching from chronic high steroid therapy to Sterazolidin, the importance of gradual reduction of steroid dosage cannot be overemphasized. It should be kept in mind that the steroid content of 8 capsules of Sterazolidin will replace 10 mg. of prednisone (or its equivalent in related steroids).

Clinical experience indicates that most patients with rheumatoid arthritis may eventually be maintained on 3 to 6 capsules of Sterazolidin a day. It is advisable to administer the total daily requirement in divided doses.

Availability Sterazolidin: Light blue and orange capsules, in bottles of 100 and 1000. (B)46-660-B

For complete details, please see full prescribing information.



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BOOKS RECEIVED

Books received by CALIFORNIA MEDICINE are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.

ALL ABOUT ALLERGY—M. Coleman Harris, M.D., and Norman Shure, M.D. Prentice-Hall, Inc., Englewood Cliffs, N.J. (07632), 1969. 368 pages, \$7.95.

A LANGUAGE STIMULATION AND READING PROGRAM FOR SEVERELY RETARDED MONGOLOID CHILDREN: A Descriptive Report—California Mental Health Research Monograph No. 11—Leanne Rhodes, M.A., Bill Gooch, Ellen Y. Siegelman, Ph.D., Charlene (Alton) Behrns, M.Ed., and Reva Metzger, B.A. Editor, Alden B. Mills. Single copies of this booklet are available on request without charge by sending request to: Alden B. Mills, Editor, Scientific Publications, California Department of Mental Hygiene, 744 P Street, Sacramento, California 95814. 102 pages; 1969.

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MENTAL HEALTH CONSIDERATIONS IN PUBLIC HEALTH—A Guide for Training and Practice—Edited by Stephen E. Goldston, Ed. D., M.S.P.H., Special Assistant to the Director, National Institute of Mental Health, Chevy Chase, Maryland. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, National Institute of Mental Health, 5454 Wisconsin Avenue, Chevy Chase, Maryland (20015), Public Health Service Publication No. 1898, May 1969. 252 pages. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, \$1.25.

MICRONEUROSURGERY—Robert W. Rand, Ph.D., M.D., Professor of Neurological Surgery, University of California School of Medicine, Los Angeles. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1969. 224 pages, with 16 contributors, 257 illustrations, including one color plate, \$25.00.

OCCUPATIONAL DISEASE IN CALIFORNIA ATTRIBUTED TO PESTICIDES AND OTHER AGRICULTURAL CHEMICALS—State of California Department of Public Health, Bureau of Occupational Health and Environmental Epidemiology, 2151 Berkeley Way, Berkeley, California (94704). 35 pages. Copies are available free upon request as long as the supply lasts from the Bureau of Health Education, California State Department of Public Health, 2151 Berkeley Way, Berkeley, California 94704.

REVIEW OF BIOCHEMISTRY—Nathan H. Sloane, Ph.D., Professor of Biochemistry, University of Tennessee Medical Units, Memphis; J. Lyndal York, Ph.D., Associate Professor of Biochemistry, University of Arkansas School of Medicine, Little Rock; The MacMillan Company, 866 Third Avenue, New York City, New York 10022. 1969; 278 pages, no price quoted.

THE MYCOPLASMATALES AND THE L-PHASE OF BACTERIA—Editor: Leonard Hayflick, Department of Medical Microbiology, Stanford University School of Medicine, Stanford, California; foreword by: Emmy Klieneberger-Nobel. Appleton-Century-Crofts, Educational Division, Meredith Corporation, 440 Park Avenue South, New York, New York 10016, 1969; 731 pages, \$30.00.

PHARMACOLOGICAL, CONVULSIVE AND OTHER SOMATIC TREATMENTS IN PSYCHIATRY—Lothar B. Kalinowsky, M.D., Clinical Professor of Psychiatry, New York Medical College, New York, New York; Hanns Hippus, M.D., Professor of Psychiatry, Free University, Berlin, Germany. Grune & Stratton, Inc., 381 Park Avenue South, New York, New York 10016; 1969; 470 pages; \$14.75.

TEXTBOOK OF PEDIATRICS—Ninth Edition—Edited by Waldo E. Nelson, M.D., D.Sc. (Hon.), Professor of Pediatrics, Woman's Medical College of Pennsylvania and Temple University School of Medicine; Attending Pediatrician, St. Christopher's Hospital for Children, Philadelphia; Associate Editors, Victor C. Vaughan, III, M.D., Professor and Chairman, Department of Pediatrics, Temple University School of Medicine; Medical Director, St. Christopher's Hospital for Children, Philadelphia; R. James McKay, M.D., Professor and Chairman, Department of Pediatrics, The University of Vermont College of Medicine; Chief of Pediatric Service, Medical Center Hospital of Vermont, Burlington, with the collaboration of 78 contributors. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105, 1589 pages; \$21.50.

CLINICAL OBSTETRICS AND GYNECOLOGY—Volume 12, Number 2—Current Diagnostic Techniques in Pelvic Cancer—Edited by Sanford Sall, M.D.; and Endoscopy—Edited by John J. Sciarra, M.D. Hoeber Medical Division, Harper & Row, Publishers, 49 East 33rd Street, New York, N.Y. (10016), 267 pages, \$22.00 per year, published quarterly, by subscription only.

DOCTORS ON HORSEBACK—Pioneers of American Medicine—James Thomas Flexner, Dover Publications, Inc., 180 Varick Street, New York, N.Y. (10014), 1969. 338 pages, \$2.50 (Paperback).

GUIDE FOR YOUNG LOVERS—George K. Morlan. A. S. Barnes & Company, Box 421, Cranbury, N.J. (08512). 148 pages, \$5.95.

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New Concepts of Digitalis

CHARLES C. WYCOFF, M.D., *San Francisco*

■ *The data presented in this review have substantiated the following ideas:*

- *There is a direct relationship between digitalis dosage and myocardial contractile force. A small dose of digitalis produces a small increase of the contractile force of the heart and a large dose increases the force of the heart's contraction by a much greater amount, whether the heart is normal, has a poor reserve, or is in frank failure.*
- *Digitalis is of benefit to the patient with cardiovascular disease whether his heart is in failure or not.*

DIGITALIS HAS BEEN RESERVED in the past to slow the pulse of a patient with a rapid ventricular response during atrial fibrillation or flutter, and to aid the heart that is in frank failure. Frequently an attempt has been made to administer a "full digitalizing dose" since there has been a belief that a dose smaller than that is not effective. Over the past decade or two a body of data has been accumulating, in the laboratory and at the bedside, which has extended the use of digitalis. It has been demonstrated that digitalis, even in low dose, increases the ability of the heart to pump out the blood that comes to it. This effect of digitalis is produced in the normal heart, as well as the heart

with pathologic changes but not in failure, and also in the heart which has failed. This paper is a review of the literature with the aim of supporting two ideas about digitalis. The first idea is that there is a direct relationship between digitalis dosage and contractile force of the heart; and the second is that digitalis is of benefit to the patient with heart disease but not in frank heart failure.

Relationship Between Digitalis Dose And Contractile Force of Heart

The idea that a "full digitalizing dose" of a cardiac glycoside must be given to achieve any effect on the myocardium has probably come from the observation that large doses of digitalis must be given to slow the ventricular response of the heart

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Reprint requests to: 900 Hyde Street, San Francisco, Ca. 94109.

during atrial fibrillation and flutter. However, that which holds true for the conduction effect of digitalis does not necessarily apply to the inotropic effect of the drug. Starr¹ summarized his views on the dose of digitalis after reviewing his studies with the ballistocardiograph in patients: "The idea of the digitalizing dose, the conception that a certain amount of digitalis, calculated from the patient's weight, had to be given before there was any digitalis action has proved wrong. This idea was based on observations made on heart rate. Measuring the forces, one finds that much smaller doses than this have definite effects on the heart's performance in many patients, often in the absence of changes of rate."

An instrument has been developed, the strain gauge, which can be sutured onto the ventricle of the heart to measure the force of the muscular contraction. This device makes it possible to assess the increase of the force of ventricular contraction produced by digitalis. In 1950, Walton et al² sutured a strain gauge to the right ventricle of normal dogs and found a direct relationship between the dose of all cardioactive drugs tested and an increase of contractile force of the heart. They found with ouabain that 0.25 of a cat unit increased the contractile force 25 percent above normal, 0.75 of a cat unit raised the contractile force 65 percent above normal and 1.25 cat units raised the contractile force 100 percent above normal. They stated: "The electrocardiograms did not show distinctive changes before development of substantial increases in contractile force. In a few instances, maximal contractile force changes preceded by a distinct interval any significant manifestation of the typical ECG changes."

Williams et al,³ in 1966, studied the contractile force of the right ventricle in normal dogs and found that 60 percent of the toxic dose of ouabain raised the contractile force 43 percent above the control level, 80 percent of the toxic dose raised the contractile force 48 percent above normal, the toxic dose raised the ventricular contractile force 65 percent above normal, and when the arrhythmia was controlled with intravenous potassium, and more ouabain was given, the contractile force rose to 84 percent above normal.

An increase of contractile force of the ventricle causes the heart to empty more rapidly. The decrease of emptying time can be used as a measure of the effect of a given dose of digitalis on the contractile force of the heart. Weissler et al,⁴ in

1965, studied 30 normal college males and measured the total duration of left ventricular systole from the onset of ventricular depolarization to the closure of the aortic valves by simultaneously recording the electrocardiogram and the phonocardiogram. Eight hours after an intravenous dose of deslanoside, they found that the emptying time had been shortened 14 milliseconds by the action of 0.4 mg of the drug, 20 milliseconds by 0.8 mg and 34 milliseconds by a 1.6 mg. They summarized their findings: "The mean response in the duration of each of the phases of systole during the first eight hours following administration of deslanoside proved to be dose-dependent."

Less than a "digitalizing dose" of lanatoside-c (Cedilanid®), 0.8 mg, has been shown to be effective in improving the cardiac status of patients with damaged hearts. Lagerlof and Werko,⁵ in 1949, administered such a dose to five patients who were in failure. They measured the cardiac output before and after digitalization and found: "The cardiac output invariably rose in the cases in heart failure while the response in the other cases sometimes was in the direction of increase, sometimes in the direction of decrease."

Malmcrona et al,⁶ in 1966, gave 0.8 mg of lanatoside-c (Cedilanid®) to ten patients who had acute myocardial infarction and a substantial fall in arterial pressure but without left ventricular failure or cardiogenic shock. They found a rise in blood pressure after the administration of the digitalis and summarized their findings: "This study indicates that a moderate digitalis dose, given intravenously to patients with myocardial infarction, may be beneficial rather than dangerous, even in the absence of overt failure, as judged from the hemodynamic effects."

It can be deduced from these studies that one of the physiological effects resulting from the administration of digitalis, an increase in contractile force of the ventricle, is dose-dependent: a small dose of the drug produces a small increase of the contractile force and a large dose results in a large increase in the contractile force of the ventricle.

Beneficial Effect of Digitalis To the Heart Not in Failure

General Considerations

Digitalis has been shown to increase the cardiac output of the heart in failure and also has been

shown to decrease the cardiac output of the heart which is not in failure.^{7,8} It was therefore assumed that digitalis was beneficial to the heart in failure and detrimental to the heart not in failure. This was an erroneous assumption regarding the heart not in failure since the fall in cardiac output is probably due to a peripheral vascular constriction that digitalis produces.^{8,9} Such vascular constriction can result in a diminished venous return to the heart and also an increased resistance to the arterial outflow.

There has been considerable experimental work in animals and observation in humans demonstrating that digitalis increases the contractile force of the heart whether it is normal, abnormal but not in failure, or in frank failure. This increase in contractile force has been demonstrated to be beneficial to the chronically stressed heart, as well as to the heart with poor reserve.

Cotten and Stopp,¹⁰ in 1958, demonstrated that digitalis increases the ability of the normal heart to pump out the blood that comes to it. They studied the effect of digitalis in normal dogs by measuring the myocardial contractile force and also by progressively increasing the left atrial pressure and measuring the stroke work as the heart load increased. They summarized their findings: "The increase in left ventricular contractile force provoked by ouabain and the higher ventricular function curves obtained after injection of this glycoside show conclusively that ouabain stimulates the non-failing heart of the dog with a complete circulatory system."

Stewart et al,¹¹ in 1938, studied 13 patients with compensated heart disease by digitalizing them over 24 hours and recording their cardiac output, electrocardiograms and heart size. They concluded that the factor common to all patients as a result of digitalis was an increase of work per beat.

Sokolow et al,¹² in 1942, studied four patients who had been in failure and were being maintained with digitalis. Discontinuing digitalis allowed them to go into failure again. To evaluate failure, these investigators used the vital capacity measurement, venous pressure, hepato-jugular reflux, circulation time, weight and clinical evaluation. They stated: "Continuous digitalization is of value in preventing recurrences of cardiac failure in ambulatory patients with sinus rhythm. It is unwise to omit this drug in patients with diminished cardiac reserve who have previously shown

failure, even though the patient is free of symptoms."

Erickson and Fahr,¹³ in 1945, studied 39 patients who had no evidence of failure but had enlarged hearts and a slowed circulation time. They found that digitalization improved the mechanical efficiency of the hearts of 87 percent of the patients studied. "We believe," they said, "that digitalis is definitely indicated for organically diseased and enlarged hearts which appear compensated, when the circulation time, as measured by the calcium gluconate arm-to-mouth method, is greater than 16 seconds."

Hedlund,¹⁴ in 1952, studied 12 patients with latent cardiac insufficiency (no overt failure) using an exercise test with determination of oxygen consumption and oxygen debt. He found that digitalization effectively decreased the oxygen consumption during work and also decreased the relative oxygen debt. He summarized, in an abstract to the author: "Therefore, it is expedient not to suspend glycoside therapy, even when the patient is in good clinical condition and is compensated. As in the case of cardiac decompensation, the patient should receive an uninterrupted treatment with the cardiac glycosides."

Braunwald et al,¹⁵ in 1961, studied 21 patients with heart disease, who were not in failure, by suturing strain gauges to their right ventricles. They found that acetyl strophanthidin increased the contractile force an average of 87 percent above control and Cedilanid® increased the contractile force 31 percent. They summarized their views: "In view of the positive inotropic effect of digitalis on the non-failing heart, the fear of cardiac depression when these drugs are used 'prophylactically' . . . would not seem to be warranted. Thus, the exhibition of cardiac glycosides does not appear to be contraindicated in patients without overt heart failure in whom the development of heart failure is feared because of the superimposition of an excessive hemodynamic burden resulting from an acute infection or surgical procedure. Indeed, the demonstration in the present study of the substantial augmentation of contractile force provided by digitalis has led to the establishment of a policy at the National Heart Institute to digitalize all patients prior to intracardiac surgery."

Selzer and Malmberg,¹⁶ in 1962, studied 15 patients who had been in left heart failure and were relieved of their frank failure by bed rest, diuretics and low salt. They recorded the patients'

cardiac pressures and performance under exercise. They observed the results before digitalization: "In all patients, the abnormal circulatory dynamics were accentuated by exercise, as evidenced by the further rise in left atrial and pulmonary arterial pressure, and an inadequate increase in cardiac output." Also they summarized the results after digitalization: "Ten patients showed significant improvement consisting of lowering left atrial and pulmonary arterial pressures and an average increase in resting cardiac output of 40 percent. Five patients showed no significant hemodynamic change."

Kahler et al,¹⁷ in 1963, studied the oxygen debt that three compensated cardiac patients developed from exercise during the time that they were not receiving digitalis, when they were receiving digitalis, and when they were receiving placebos, in various sequence. "All had inactive rheumatic valvular disease, cardiomegaly, and a history of cardiac decompensation some months or years previously, but had none of the clinical signs of congestive heart failure at the time of the study. These three patients were selected because they were capable of performing light physical activities without cardiac symptoms in the absence of digitalis therapy." The authors summarized their findings and opinions: "In all patients the oxygen debt was smaller during the period of digoxin administration, although the external work performed was identical. . . . The accumulation of a smaller oxygen debt following exercise while these subjects were receiving digoxin indicates that the functional status of their circulatory system was improved by the drug. . . . It would appear that digitalis administration is beneficial to at least some patients who have cardiac disease and enlarged hearts and some decrease in cardiac reserve without signs or symptoms of heart failure."

Mason and Braunwald,¹⁸ in 1963, studied ten patients when they were not digitalized and when they were digitalized. They found that digitalis increased the myocardial contractile force in those unanesthetized humans with a normal heart and those with an abnormal heart that was not in failure. They studied the rate of change of the intraventricular pressure which is an index of the contractile force of the heart. They summarized their findings: "In four patients without heart disease and in two patients with minimal cardiac abnormalities and normal right ventricular function, 0.30 to 0.60 mg ouabain elevated the right

ventricular peak rate of change (dp/dt) by 9.9 to 73.5 percent (average = 31.5 percent of control values). In four patients with uncomplicated atrial septal defects, in whom the left ventricular hemodynamic burden and left ventricular function were normal, 0.60 mg ouabain elevated the left ventricular peak dp/dt by 26.3 to 48.8 percent (average = 35.5 percent) of control value. These observations in intact, unanesthetized subjects indicate that ouabain is capable of stimulating the contractility of the non-failing and of the normal human heart."

Murphy et al,¹⁹ in 1964, studied nine patients with cardiac disease by catheterizing the right and left (transseptal) sides of the heart. Three of the patients were in heart failure and six were compensated. Various indices were studied before and after digitalization—cardiac index, stroke index and stroke work, stroke power, mean systolic ejection rate, left ventricular end-diastolic pressure, first derivative of left ventricular systolic pressure (dp/dt), mean systolic ejection period, systemic arterial pressure and ventricular function points. They commented on their findings: "It is of clinical interest that evidence of augmented ventricular performance was found in our patients with cardiomegaly but no detectable clinical heart failure. Improvement of ventricular performance in these cases after digitalization was characterized mainly by an increase in the rate of rise of left ventricular pressure and a general tendency of ventricular function points to shift left and upward on the stroke work-left ventricular diastolic pressure diagram."

Sonnenblick et al,²⁰ in 1966, studied six patients who had previously had operations on the heart but were in a compensated state. Metal clips had been sutured to the ventricular surface so that cineradiographs could be taken to record the velocity of contraction and this rate was related to the force of contraction as determined by the arterial pressure. The studies were done before and after digitalization. They summarized their findings: "It was observed that ouabain always augmented myocardial contractility as reflected in the force-velocity relation. Velocity of shortening increased an average of 77 ± 5 (SEM) percent. . . . It is concluded that the fundamental action of digitalis glycosides is to augment the contractile state of the heart, whether normal or failing, but that in the absence of heart failure this improve-

ment is not translated into an increase in cardiac output."

Reindell and Konig,²¹ in 1967, reported on studies of several hundred volunteers and patients during which they determined the myocardial reserve by doing exercise tests. During the exercise tests, they measured the heart rate, the heart size and the oxygen uptake. They found that patients who were not in failure but who had fixed hypertension, coronary insufficiency or branch blocks, or who had had myocardial infarction, showed performance tests that were well below the normal for their ages. In other words, a "loading insufficiency" developed. These patients were shifted to the normal or near normal status by digitalization. These investigators summarized their studies: "According to these findings there is no doubt that the uneconomical mode of operation of the heart which becomes insufficient of loading is decisively improved due to application of digitalis. This results in the basic demand that the heart which is insufficient on loading should be digitalized in the same way as the heart which is insufficient at rest."

Mason,²² in 1968, summarized the mode of action of digitalis: "Since digitalis has the same fundamental action on both normal and failing hearts, the view that the drug has a harmful effect on the non-failing heart cannot be given credibility. Digitalis lowers the oxygen debt following exercise in patients with cardiomegaly but without heart failure, indicating that the functional status of the circulatory system may be improved by the drug in at least some patients without overt failure. In addition, digitalis may be of potential clinical value in preventing the development of ventricular hypertrophy in patients with aortic valvular disease or hypertension without heart failure, since the drug reduces the degree of mortality from heart failure and the degree of ventricular hypertrophy resulting from a chronic pressure load in experimental animals, further, the belief that the administration of digitalis in special situations may be helpful in certain cardiac patients without failure is gaining in prevalence. Thus, prophylactic digitalization may protect the myocardium in these patients in the face of the depressing effects of anesthesia and operation, serious illnesses such as pneumonia, and the hypervolemic state during pregnancy."

The benefit of digitalis to the acutely stressed heart of the dog was shown by Selzer et al,²³ in 1953. During thoracotomy, they measured the

amount of constriction that could be applied to the pulmonary artery and the length of time the constriction could be tolerated before failure occurred. The studies were done before and after ouabain was administered. They stated: "It seems reasonable to conclude from the results of this study that the group of digitalis drugs may exert a favorable effect upon the normal heart during unusual stress. It seems difficult to visualize a clinical situation where such a property of digitalis would appear useful. However, if a similar action could be demonstrated upon the competent hypertrophied heart, where such an effect could conceivably be much more useful, then earlier prophylactic use of digitalis could be justified in compensated heart disease."

In 1908 and 1929, Cloetta^{24,25} found that digitalis prevented the chronically stressed rabbit heart from enlarging as much as the undigitalized stressed heart. He avulsed a single aortic valve in the animals and maintained half of the group on digitalis. At the end of one year, the untreated animals had an increase of heart size 80 percent above the normal unstressed rabbit heart and the digitalis-treated animals had only a 38 percent increase of heart size above normal. In addition, acute performance tests of the hearts were made and the results were summarized: ". . . one finds that the crippled digitalis treated heart is almost equal to the normal; while the defective heart without digitalis treatment is much more rapidly exhausted. The capacity of the former is nearly double that of the latter, a fact of great importance in practice. This should be sufficient to induce prophylactic treatment with digitalis in all early cases of endocarditis which are apt to terminate in valvular lesions."

Williams and Braunwald,²⁶ in 1965, studied chronic heart strain in rats by constricting the abdominal aorta, which resulted in hypertension. Some of the rats were maintained on digitalis. Their results were similar to those of Cloetta. Fewer of the digitalized rats died from heart failure and the weight gain of the digitalized hearts was less than the undigitalized hearts.

Preoperative Digitalis Benefits The Patient with Myocardial Disease

The stress of surgical operation on the myocardium is considerable with frequent occurrence of hypoxia,²⁷ hemorrhage, and depression from

anesthetic drugs.²⁸ These strains are detrimental to the patient with myocardial disease, as revealed by a high incidence of postoperative cardiac complications. Sufficient data have now been accumulated to show that preoperative digitalization protects the hearts of those patients who have cardiac disease but are not in failure.

The thoracotomy patient

Wheat and Burford,²⁹ in 1961, reported on a retrospective study of 439 patients who had thoracotomy. These investigators summarized their findings: "Cardiac complications following major intrathoracic resections can be reduced from 20 to 10 percent over the age of 55 by prophylactic preoperative digitalization. . . . All patients over 60 years of age in whom a major intrathoracic resection is contemplated should be digitalized routinely preoperatively."

Heilbrunn and Hardin,³⁰ in 1963, retrospectively reviewed 89 patients over 70 years of age who had thoracotomy. They found that non-digitalized patients had a 24 percent incidence of postoperative arrhythmia and the arrhythmia caused or contributed to the death of 4 percent of the total number of undigitalized patients. The patients who had been digitalized preoperatively had a postoperative incidence of arrhythmia of 1 percent which did not contribute to or cause fatality. Heilbrunn and Hardin summarized their results: "We believe that prophylactic digitalization is indicated in patients over 70 who undergo thoracic procedures and is of value in avoiding and controlling postoperative arrhythmias."

Bergh et al,³¹ in 1967, retrospectively reviewed 229 cases of pneumonectomy, in 148 of which the patients had had prophylactic digitalization. The incidence of postoperative atrial fibrillation was 10 percent in the digitalized group and 20 percent in the non-digitalized. The patients were digitalized on the day of operation after surgery had been completed.

Burman,³² in 1965, reported on 244 patients over the age of 40 who had major thoracic surgical procedures without extracorporeal circulation. One hundred and fifty-nine of them were digitalized to the limit of tolerance and 85 were either incompletely digitalized or not digitalized at all. The incidence of arrhythmias or congestive failure that occurred during the first three weeks postoperatively in the fully digitalized group was 3.2 percent and in the other group was 16.4 percent. The

mortality from cardiac complication in the fully digitalized group was 1.3 percent and in the other group was 7 percent. Burman also reported on the results with cardiac operation with and without extracorporeal circulation. He stated: ". . . It is far safer to digitalize a patient unhurriedly four or five days before surgery . . . than to do so haphazardly in the face of impending disaster." In summary he stated: "Each group was divided into two categories, those who received preoperative digitalization and those who did not. The subsequent course of each group was compared and found to be strikingly dissimilar in favor of those receiving preoperative digitalis."

The general surgery patient

Brockner and Christiansen,³³ in 1965, reported on 235 patients who had surgical operation for malignant disease of the stomach. In some of the patients arrhythmias and heart failure which required digitalization developed in the postoperative period. Of the group with no pre-existing cardiac disease, 4 percent required digitalization after the operation. Of the group with cardiac disease but not in heart failure preoperatively, 50 percent required digitalization after the operation. The authors stated: "The conclusion is drawn that digitalis should be administered before major operations if one or more of the following abnormalities is present: (1) a history of cardiac symptoms; (2) electrocardiographic changes suggestive of myocardial degeneration; (3) enlargement of the heart demonstrated by roentgen examination of the thorax."

McCord,³⁴ in 1967, did a retrospective study of 186 patients over 60 years of age who had partial colectomy. Sixty-eight of them were found to have coexistent cardiovascular disease. Thirty-nine of the patients with coexistent cardiovascular disease were not digitalized. The morbidity rate for this group was 46 percent and the mortality rate was 18 percent. Twenty-nine patients were digitalized preoperatively. The morbidity in this group was 17 percent and the mortality was 7 percent. McCord summarized his results: "The findings in this study suggest that each elderly patient who is to have a major surgical procedure should be evaluated for the presence of cardiovascular disease. If evidence of such disease is found, the morbidity and mortality from postoperative cardiovascular complications can be reduced by the use of prophylactic digitalization."

Effect of Digitalis in Shock

Data have been accumulating that reveal digitalis is of benefit in hypotension resulting from trauma, hemorrhage, infection, anoxia, and anesthesia.

Keyl and North,³⁵ in 1957, found that pretreatment of rats with digitalis was effective in lowering the mortality rate from traumatic shock produced by tumbling.

Crowell and Smith,³⁶ in 1964, bled 100 dogs to shock levels and measured the oxygen deficit developed by the shock as an assessment of the degree of shock. The blood that had been withdrawn was reinfused after the pre-determined oxygen deficit was produced and half of the animals were then digitalized. At an oxygen deficit of 140 ml per kg, all the digitalized animals survived and all the undigitalized died.

Baxter et al,³⁷ in 1966, demonstrated a myocardial depressant factor in the blood of dogs that had received a 50 percent skin burn 24 hours before cross circulation with normal dogs. The blood of the burned animals produced a 53 percent fall of cardiac output in the normal animals within five minutes after the start of perfusion. These animals were not treated to assess the effect of digitalis on the fall of cardiac output. However, Brand and Lefer,³⁸ in 1967, found a myocardial depressant factor produced in the blood of cats by hemorrhagic shock. They were able to completely counteract this factor with digitalis. They used the cat papillary muscle as the test device.

Levin and Painter,³⁹ in 1966, reporting on 28 soldiers (ages 17 to 24 years) treated for meningococcal disease, noted that ten had hypotension which responded in most instances to digitalis. They summarized: "Previous emphasis on peripheral vascular collapse in the etiology of shock in this disease has been at least partially misplaced. A primary decrease in cardiac output appeared to be a major factor in the hypotension seen in the majority of cases in this series. Recommended management of hypotension includes placement of a central venous catheter with continuous monitoring of central venous pressure, intravenous administration of a rapidly acting digitalis preparation in full digitalizing dosage with electrocardiographic monitoring, and use of a continuous isoproterenol infusion to maintain cardiac output in those patients not showing adequate response to digitalis alone."

Hernandez et al,⁴⁰ in 1968, used excised atrial muscle of non-failing human hearts as test systems. In 11 cases the heart had not been digitalized and in 15 it had been digitalized before the atrial strips were excised. The muscle strips were pre-oxygenated for one hour, rendered hypoxic for one hour, and then aerated for one hour. Measurement of the contraction response was recorded throughout. Following anoxia, the undigitalized strips recovered 30 percent of the equilibration contraction level, but the predigitalized strips recovered 62 percent of the equilibration level.

Goldberg et al,⁴¹ in 1962, found that halothane caused a progressive arterial hypotension and decrease of the contractile force of the dog heart with deepening anesthesia. A concentration of 0.2 percent halothane depressed the contractile force by 33 percent, 1 percent halothane depressed the contractile force 73 percent, and 2 percent halothane depressed the contractile force 80 percent. They did the same studies after digitalization and summarized: "Pretreatment with digoxin significantly diminished the negative inotropic and hypotensive effects of 1 and 2 percent halothane anesthesia."

Digitalis Protects in Coronary Occlusion

Cronin and Zoster,⁴² in 1965, produced cardiogenic shock in 23 dogs by coronary embolization and then digitalized some of the animals. They summarized their results: "Rapid digitalization . . . caused a substantial elevation in arterial blood pressure and cardiac output in every animal. . . . This restoration of the shocked animals' hemodynamic status toward normal was associated with a marked increase in left ventricular work in all dogs and an average lowering of the end-diastolic left ventricular pressure. . . ."

Marano et al,⁴³ in 1966, used a comparable technique of coronary embolization in 28 dogs to produce cardiogenic shock. Ouabain produced a significant rise of cardiac output, central aortic pressure and dp/dt in ten of eleven animals. They summarized their findings: "It is concluded that rapid digitalization may be of definite, though transitory, benefit in improving cardiac output and aortic pressure in acute myocardial infarction with shock, even in the absence of hemodynamic evidence of congestive heart failure."

Aldinger,⁴⁴ in 1967, prophylactically digitalized 24 dogs and then occluded the artery to the left ventricle. Ventricular fibrillation occurred in 63

percent of the non-digitalized dogs but fibrillation occurred in only 25 percent of the predigitalized dogs. In addition, he stated: "The digitalized animals developed and maintained more myocardial tension than the untreated group when subjected to the stress of acute coronary occlusion."

Malmborg,⁴⁵ in 1965, reported on a study of 38 men, aged 40 to 58, who had symptoms of coronary insufficiency but were not in apparent heart failure. He stated: "The results indicate that even at rest acute digitalization had a small but significant effect on both the flow and the intracardiac pressures. During exercise the effect was more marked as evidenced by a highly significant lowering of the heart rate." His data show that some patients were in occult failure at rest and others went into failure with exercise, and digitalis aided both these groups. He summarized: "A beneficial effect of digitalis upon the hemodynamics could be demonstrated in 57 percent and on the subjective symptoms in 53 percent of the studied cases. . . . The present results prove that digitalis therapy was actually of value in the therapy of a certain number of patients with coronary heart disease even when clinical signs of congestive failure were lacking."

Discussion

These data show that small doses of digitalis increase the contractile force of the heart and larger doses produce an even greater increase in the contractile force. Also these data show that digitalis is beneficial to patients who have heart disease but are not in frank heart failure.

A very important clinical application of these ideas is the prophylactic digitalization of patients with cardiac disease who are not in heart failure and are to have an operation. These data show that such patients who are digitalized have a lower incidence of morbidity and mortality than the patients with cardiac disease who are not digitalized preoperatively.

Heilbrunn and Hardin³⁰ expressed belief that all patients over the age of 70 should be digitalized preoperatively if they are to have thoracotomy. Their patients over 70 years of age who had preoperative digitalization had a decidedly lower incidence of cardiac arrhythmia and mortality therefrom than did those who were not digitalized preoperatively. Burman³² also found a pronounced lowering of cardiac complications and mortality therefrom in patients with thoracotomy who were

completely digitalized before operation. In addition, he pointed out the desirability of slowly digitalizing the patients preoperatively rather than hurriedly doing so when the cardiac complications occurred. Brockner and Christiansen³³ found that patients who were not in heart failure and were operated on for malignant disease of the stomach were 12 times as likely to need postoperative digitalization if they had a history of cardiac symptoms, or had electrocardiographic changes suggestive of myocardial degeneration, or enlargement of the heart as seen roentgenographically. In addition, these observers recommended preoperative digitalization if one or more of these findings were present even though the patient had no sign of heart failure. McCord³⁴ found that patients over 60 years of age who had cardiovascular disease and underwent partial colectomy had morbidity and mortality rates halved by preoperative digitalization. He considered the patients to have cardiovascular disease if there were positive findings in two of four items of examination: history, physical examination, roentgenogram and electrocardiogram. An isolated finding of electrocardiographic evidence of an old myocardial infarction also established a diagnosis of cardiovascular disease.

The stresses that the patients are subjected to during operation are many. Some that are particularly detrimental to the cardiovascular system are the diminution of tissue perfusion resulting from blood loss, the hypoxia that results from diminished respiration, and the depression of the myocardium resulting from the action of the anesthetic drugs. These stresses are partly responsible for the high incidence of morbidity and mortality that occurs during and after operation in patients who have preexisting cardiovascular disease. Even with the best of management these stresses occur all too frequently. It is possible to lower the incidence of morbidity and mortality following operation by preoperative digitalization of patients who have evidence of cardiovascular disease.

Another clinical application of some of the above summarized data is in the patient with chronic hypertension. In such a patient a constant increase in work load is put on the heart, which may eventually result in myocardial hypertrophy. Digitalis, by increasing the contractile force of the heart, can reduce hypertrophy and failure when chronic stress is put on the heart, as was demonstrated by Cloetta²⁵ and Williams and Braunschweig.²⁶ These investigators stressed the hearts of

animals by avulsing one aortic valve leaf in one series and constricting the abdominal aorta in the other series. Digitalis limited the resultant myocardial hypertrophy and reduced the mortality from heart failure. The same physiological principles should apply to the stress of chronic hypertension in humans. Therefore, hypertensive patients should have longer lives and less disability when maintained on digitalis.

Reindell and Konig²¹ showed that the function of the heart is diminished in patients who have had myocardial infarction and apparently have recovered. These investigators also found that digitalis was effective in returning the function of hearts damaged by myocardial infarcts back to a near normal level. Another observer, Malmberg,⁴⁵ found that digitalis had a beneficial effect on the hemodynamics and subjective symptoms of patients with coronary insufficiency. Apparently the increase of contractile force produced by digitalis causes a better perfusion of the ischemic heart as well as the heart damaged by a myocardial infarct.⁴²⁻⁴⁵ Digitalis is of benefit when given to the patient who has angina, an acute myocardial infarction⁴⁶ or a healed myocardial infarct, even when the heart is not in failure.

Toxicity is the major deterrent to the use of digitalis. It is known that arrhythmias produced by digitalis can be lethal to the patient with heart failure, particularly when a low level of potassium is present in the blood.⁴⁷ Also, it has been shown in animal studies that a dose of digitalis that produces an arrhythmia can decrease the flow of blood in the coronary artery.⁴⁸ Therefore, the dose of digitalis should be kept below the arrhythmic dose. It is imperative that the dose of digitalis be individualized for each patient. The "digitalizing dose" has been assessed as 60 percent of the toxic dose.^{49,50} However, it is now recognized that even small doses of digitalis have a positive inotropic effect on the heart and produce an increase in the contractile force. Therefore, it is possible to get a beneficial effect from digitalis in a dose much lower than that which was considered a digitalizing dose in the past. When the maximum effect of digitalis is desired, the dose can be raised slowly, preferably over days, until toxicity occurs and then a slightly lower dose can be administered. Nausea, vomiting, yellow vision or scotomata will occur frequently as a symptom of toxicity before arrhythmias occur. However, the pulse must be checked for ectopic beats, bigeminy and runs of tachy-

cardia, and the electrocardiogram can be watched for prolongation of the PR interval or for frank A-V dissociation. Many patients do not have gastrointestinal or nervous system changes before arrhythmias.

A "full digitalizing dose" may become a toxic dose if a patient goes into failure. Olson et al,⁵¹ in 1955, reported a study which showed that in dogs with heart failure ventricular tachycardia developed with one-third the dose of cardioactive drug that was needed to produce the same degree of toxicity in normal dogs. These investigators did not report the blood level of potassium in the animals studied.

Other situations besides decompensation that make the heart more sensitive to digitalis are low level of serum potassium, high level of calcium, hypoxia, oliguria, acute myocardial infarction, and individual variation.⁵²⁻⁵⁹

The idea that a "full digitalizing dose" must be given to produce a beneficial effect on the heart presupposes that the only effect of digitalis is the slowing of the rate of the heart in failure and arrhythmias. It is now known that the increase in contractile force is the primary beneficial effect of digitalis and the slowing of response of the ventricle in atrial fibrillation and flutter is one of the lesser effects. Even small doses of digitalis produce an increase of contractile force, whereas much larger doses are required to achieve a ventricular slowing in atrial fibrillation.⁶⁰ The administration of doses of digitalis smaller than those required to slow the ventricle in atrial fibrillation are effective in improving the function of the heart. The smaller doses of digitalis should not be considered as homeopathic doses.

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Learning Disorders as a School Health Problem

Neurological and Psychiatric Aspects

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■ *Broadened concepts of intellectual functions have shown that many varieties of mental subnormality may be preventable or subject to improvement with proper treatment. Many types of neurologic dysfunction are accompanied by learning disorders based on specific intellectual deficits.*

A more refined delineation of the higher cerebral functions of each child with a learning disorder provides the basis for improved specific remedial educational techniques. Such detailed assessment of higher functions of the nervous system can be greatly enhanced by the appropriate special evaluations carried out by well trained psychologists, speech pathologists and educational consultants, working in cooperation with physicians.

The varieties of adjustment problems of children and emotional impact of a learning disorder should be recognized as early as possible and treated appropriately. Motor and perceptual-motor therapies may have limited value in some cases but may be harmful if indiscriminately applied. Psychotropic drugs have a relatively limited place in the management of learning disorders but may be immensely valuable in some cases by helping to control specific behavior problems which interfere with learning processes.

Physicians have a major responsibility to provide help and leadership in dealing with learning disorders.

MOST ESTIMATES PLACE the incidence of mental retardation, as customarily defined on the basis of an intelligence quotient score below 70 on a standard test, at approximately 3 percent of the total population.^{88, 114} However, Zigler has pointed out that the actual incidence of mild grades of mental retardation appears to be much greater than would be predicted on the basis of a theoretical distribution pattern for "intelligence" in our society.¹⁴³ Many borderline forms of mental subnormality are often more obscure and undiagnosed. These milder learning difficulties afflict a much larger group of children, probably eight to ten times greater than the number with more obvious, more profound degrees of mental retardation.^{52,77}

In a broad sense, the concept of mild mental retardation may be properly extended beyond the usual simple I.Q. classification (50 to 70) to include children with specific, often severely handicapping learning disabilities, such as "developmental dyslexia," despite an I.Q. score lying within the "normal" range or higher. This broader concept incorporates the definition of intelligence on a multilateral pattern of learning and memory and performance functions which may be pliable and subject to modification in various ways. It contradicts the older notion of intelligence as a more or less unitary level of capacities which remain static, rigidly fixed for each individual, from early infancy. It contradicts and condemns the traditional sterile doctrine of viewing mental retardation as "an unmodifiable cerebral condition which led to incurable behavioral inadequacy"—that is, a global intellectual subnormality.¹⁵

The importance of this subject lies not only in its present and apparently increasing prevalence, but also in the generally higher individual potential which may be realized through the earliest possible detection, adequate evaluation, and appropriate remediation. It has been amply demonstrated that mild mental subnormality, when neglected or mishandled, plays a heavy contributory role in psychiatric illness, addiction, delinquency, crime, and other economic waste.^{87,103,104}

Children with milder learning disorders often present difficult problems to physicians, both in

public health settings and in private practice. All physicians should work vigorously toward a more sophisticated understanding of these problems.^{52,61,108}

Etiology

That learning problems may result from many causes has been increasingly apparent. Traditional views of the classification of mental retardation as *either* exogenous *or* endogenous have been largely replaced by a broader understanding of the many factors which influence learning processes.^{61,81}

These potential etiologic factors include ethnic and cultural influences, socio-economic status, educational facilities, family relationships, individual temperament and behavior patterns, and emotional and motivational factors, as well as a large variety of more subtle disorders of the central nervous system.⁵²

Cultural-Familial Retardation

By far the largest group, the "cultural-familial" form of mild mental subnormality is practically confined to socio-economically and educationally disadvantaged families. The long-standing question in these cases about the relative etiologic importance of hereditary and environmental factors remains largely unsettled, along with the question about whether these individuals really differ essentially from the normal population in the qualitative aspects of their cognitive functions.¹⁰³

Quite often, gross deficiencies in parental care and training of children are encountered in disadvantaged families.⁷⁹ As enumerated in a recent report by the Group for the Advancement of Psychiatry,⁶¹ specific sociocultural factors related to the family setting include the following:

- Insufficient or discontinuous mothering with physical neglect.
- Distorted patterns of child rearing with psychotic or retarded parents.
- Family disorganization: absent members; antisocial behavior in one or more family members.
- Social isolation of family and family members.
- Poverty, crowding, noise, lack of privacy, preventing personal ownership and control of physical *objects* (toys, games, books, clothes, beds), as well as control of *space* and *time*.

Many slum children come to school with dialectic differences and also with behavior patterns which have been essential to their growth and sur-

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vival within their home or neighborhood environment. Their heightened distractibility and limited techniques for impulse control may seriously interfere with ordinary classroom learning. Other subtle perceptual and conceptual deficits frequently complicate the learning problems of these children.²³

Brain Damage

Aside from possible hereditary neurological weaknesses, socioculturally disadvantaged children generally have a high risk of organic factors as a result of nutritional inadequacies, gestational insults, postnatal infection, cerebral trauma, and frequently substandard medical care. Similar subtle and generally unrecognized structural damage of the brain also occurs during the fetal and perinatal life of children in middle and upper economic class families.^{88,94}

In a retrospective study Kawi and Pasamanick showed that complications of pregnancy, premature birth, and abnormalities of the prenatal and paranatal periods were far more frequent among cases of reading disability than among controls. Particularly important factors were found to be the toxemias of pregnancy (pre-eclampsia, hypertensive disease), bleeding before the third trimester, placenta praevia, and premature separation of the placenta. Kawi and Pasamanick concluded that "there is a continuum of reproductive casualty with a lethal component consisting of abortions, stillbirths, and neonatal deaths, and a sublethal component consisting of cerebral palsy, epilepsy, mental deficiency, and behavior disorders in children."^{69,70}

Recently Towbin reported correlations of clinical case material with over 600 fetal (stillborn) and neonatal brain specimens studied, using a technique of whole-brain serial histologic section, which made possible the consistent identification and the geographical localizations of focal lesions, large and small.¹³² He showed that two types of damage commonly occur: (1) in the premature fetus and newborn (25 to 35 weeks gestation), the usual hemorrhagic infarction chiefly involves the periventricular white matter and basal ganglia, due to the vulnerability to hypoxia of the highly vascular deep, rapidly developing deposits of germinal matrix tissue; (2) in infants born at full term the cerebral cortex is relatively more vulnerable to hypoxic damage because of the shift of biologic activity and vascularity during this stage of maturation.

Towbin's study provides evidence that neonatal cerebral damage often has its origin prior to labor. These pathological findings indicate that the frequent and paradoxical occurrence of cerebral palsy and organic mental retardation in infants having a history of uncomplicated non-cyanotic delivery may be due to prenatal cerebral hypoxic damage.

Towbin pointed out that lesser degrees of hypoxic injury may escape detection even microscopically, that the depletion in the nerve cell population may be subtle and unrecognizable. An overall loss of neurons up to 10 percent cannot be easily adjudged, even though the loss may amount to millions of nerve cells. The most differentiated, most highly specialized neurons are the most vulnerable ones of the entire body to hypoxic injury.¹³²

While lethal prenatal cerebral lesions contribute heavily to the high incidence of neonatal mortality, lesser grades of hypoxic prenatal cerebral damage may be largely asymptomatic during infancy. Delays in language and motor development may be the first clear indications of subtle cerebral dysfunction and future learning problems based on prenatal cerebral damage.¹³⁹

Genetic Abnormalities

In recent years a number of chromosomal abnormalities have been identified in some relatively uncommon syndromes which are accompanied by mental subnormality,^{22,25} also several inborn errors of metabolism which critically affect cerebral function have been described and delineated.¹¹¹ These studies have shown clear indications that some varieties of severe mental retardation may be preventable with early diagnosis.^{52,111} Many issues have been raised by these studies, and many questions about the role of hereditary factors in learning disorders still remain unanswered.^{7,44}

Specific Learning Disorders

"Specific developmental dyslexia" probably has been the most intensely studied, as well as the most controversial specific learning disorder. This condition was first reported in 1896 by a British general practitioner, W. Pringle Morgan,⁹⁹ as "A Case of Congenital Word Blindness." Morgan wrote:

Percy F.—a well-grown lad, aged 14 . . . is the eldest son of intelligent parents, the second child in a family of seven. He has al-

ways been a bright and intelligent boy, quick at games and in no way inferior to others of his age. His greatest difficulty . . . his inability to learn to read . . . is remarkable, and so pronounced, that I have no doubt it is due to some congenital defect. He has been at school or under tutors since he was seven years old, and the greatest efforts have been made to teach him to read, but in spite of this laborious and persistent training, he can only with difficulty spell words of one syllable . . . The schoolmaster who has taught him for some years says that he would be the smartest lad in the school if the instruction were entirely oral . . .

Many other case reports appeared during the next few decades, especially by ophthalmologists, who were often the first physicians consulted about failure to learn to read.³⁶ In the first monograph on this subject, published in 1917, James Hinshelwood, a Scottish eye surgeon, reviewed his personal series of 31 cases gathered over a period of nearly 20 years. Hinshelwood regarded this as a relatively uncommon hereditary defect "occurring in children with otherwise normal and undamaged brains."⁶⁷

The first comprehensive study of neurological and psychiatric aspects of specific reading disability was made by an American, Samuel T. Orton. In his classic monograph, published in 1937, Orton emphasized the relationship of reading disability to other developmental language disorders, congenital dyspraxia, and ambiguous or confused handedness.¹⁰¹

Following Orton's studies, Paul Schilder and Lauretta Bender developed the concept that developmental dyslexia is a manifestation of disturbed Gestalt function and an accompanying lag in cerebral maturation.^{10,12,115} More recently, Drew reported an intensive neurological evaluation of three dyslexic individuals in one family. His findings suggested that parietal lobe involvement was the anatomic substrate for a general disturbance in Gestalt function.³⁹

Several extensive medical studies by Scandinavian workers, particularly those by Skydsgaard,¹²⁶ Hallgren⁶³ and Hermann,⁶⁶ emphasized the essentially "pure" or specific nature of developmental dyslexia, which they regarded as an hereditary nosological entity. Hallgren concluded from a clinical study of 276 cases the specific dyslexia follows a monohybrid autosomal dominant mode of inheritance with almost complete manifestation.

Since the pioneer multidisciplinary research

report on reading disorders in 1954 by Ralph Rabinovitch and his colleagues at the University of Michigan,¹⁰⁹ there has been rapid growth of interest in medical research in this field. Within the present decade, President John F. Kennedy's vigorous leadership and concern over mental retardation marked the start of a new era of public involvement.¹⁰³

An enormous amount of evidence has accumulated, relating learning disorders to linguistic, perceptual and other developmental neurological functions.^{37,54,90,97} However, despite this growth of knowledge, there has been considerable resistance to the acceptance of neurological factors as etiologically significant.¹⁰⁶ Conversely, other investigators have extended neurological theory beyond established boundaries to provide rationalizations for faddist remedial techniques.^{90,97}

Additional diagnostic perplexity has arisen from the multitude of terms used in various national, state, and local school programs to designate special classes for children who are classified as "educationally handicapped" (EH), "neurologically handicapped," (NH) "perceptually handicapped," or "mentally exceptional."

Many educators and psychologists have opposed all medical concepts of learning disorders, and have resisted the use of terms with medical implications, such as congenital word-blindness, specific language disability, strephosymbolia, developmental dyslexia, and minimal brain dysfunction. Their objections include (1) an unwillingness to consider any hypothesis which relates "milder" learning disorders to cerebral dysfunction; (2) failure to find proof that developmental dyslexia exists as a pure nosological entity affecting any substantial number of children; (3) failure to find any differences between dyslexic children and normal readers in the types of errors made in reading; (4) the great variation in frequency of reading disability in different classes; (5) the usual concurrence of reading disabilities with other defects, and (6) the belief that reading and other language disabilities "should be regarded as phenomena which fall within the framework of normal variation."⁸⁶

Recognizing this controversy, Shankweiler¹¹⁸ recently wrote:

Developmental dyslexia clearly should not be regarded as a unitary condition. Just as there are a number of acquired cerebral syndromes in which dyslexia is a prominent symptom, developmental syndromes occur which include reading disabilities of varying

degrees of purity. Developmental dyslexia is necessarily a rather broad concept which refers to a number of types of reading disability which may or may not be related in etiology and in the underlying disturbance of function. The term "developmental dyslexia" is worth retaining, because it refers to a group of disorders which are profitably to be distinguished from the mass of cases of reading backwardness. Clearly, a careful delineation of the various dyslexia syndromes is of the greatest importance for treatment. At present there is little solid knowledge of any of these syndromes and only hints as to ways in which different types of reading disability are linked to salient features of development.

At its meeting in Dallas in April 1968, the World Federation of Neurology's Research Group on Developmental Dyslexia and World Illiteracy, under the leadership of Dr. Macdonald Critchley, formulated and unanimously approved the following definitions:

1. *Specific Developmental Dyslexia*: A disorder manifested by difficulty in learning to read despite conventional instruction, adequate intelligence, and socio-cultural opportunity. It is dependent upon fundamental cognitive disabilities which are frequently of constitutional origin.

2. *Dyslexia*: A disorder in children who, despite conventional classroom experience, fail to attain the language skills of reading, writing, and spelling commensurate with their intellectual abilities.^{13,4}

In addition to developmental dyslexia, other specific learning disorders are related to deficits in other symbolic functions and intellectual capacities, such as directionality, space-time perception, abstract conceptualization, attention span, and impulse control.³³ Specific writing disability (dysgraphia) may be a practically isolated type of motor deficit, although it often is part of a more diffuse "clumsy child syndrome," or a "congenital dyspraxia."⁶² Most cases of "specific" learning disabilities show mixtures of such deficits. Each child presents a unique pattern of symptoms and a complex mixture of relative weaknesses and strengths.³²

Neurological Studies

During recent years considerable effort has been devoted to the development of more refined techniques for the neurological examination of children with learning and language disorders.³⁶ Many reports have described the possible diagnostic value of various equivocal or "soft" signs, which are

often found in these cases in an expanded neurological examination.^{4,19,27,31,38,123,124,125} There is need for further standardization and evaluation of many of these equivocal but apparently useful techniques. Some of these "soft" signs include an isolated pathologic toe sign, reflex asymmetry, mild ataxias, tremors, clumsiness, mild hearing defect, and abnormality of extraocular movements. Several of the older neurological tests of higher cerebral function have also recently been studied more intensively in children with learning disorders. These include:

- Synkinesis, also known as abnormal associated movements, mirror movements, or adventitious overflow movements^{1,30,47}

- Arm extension test^{27,121,125}
- Head rotation test^{27,121}
- Dual simultaneous sensory testing^{13,78,144}
- Imitation of gestures¹⁷
- Right-left orientation^{9,14}
- Finger identification and localization^{14,75,76}
- Choreiform syndrome^{93,107,112}

A recent study in England on the visuo-motor abilities of 810 healthy school children brought to light 54 cases (6.7 percent) in which performance was so deficient as to suggest a specific developmental failure. The children with visuo-motor impairment were significantly inferior to controls in a series of tests of spatial judgment and manual skill; they showed a variety of educational problems, especially in spelling and arithmetic. This carefully conducted study supports the view that agnosic-apraxic disabilities in otherwise normal children are "by no means rare and warrant wider recognition."²⁰

One-half or more of children with learning disorders reported in various studies have shown significant electroencephalographic abnormalities.^{8,31,72} Focal dysrhythmia, especially parieto-occipital, is common. In other cases the dysrhythmia is more diffuse. Obviously, a diagnosis of a learning disorder cannot be made from the electroencephalogram, and a normal electroencephalogram does not rule out a learning disorder.^{2,6,58,71,140}

The value of the electroencephalogram in these conditions lies in (1) providing more complete evaluation of the nervous system, (2) confirmation of the "organic" nature of the learning disorder in some instances, (3) ruling out a hidden seizure disorder, (4) providing a baseline for future re-evaluation, and (5) better insuring the safety of a trial of activating medications which may at times

precipitate seizures (for example, deaner, phenothiazines).

Minimal Brain Dysfunction

Recently the term *minimal brain dysfunction* has been more or less officially adopted in this country for a large group of borderline problems of children, including specific learning disabilities, as recommended in a study sponsored by the National Institute of Neurological Diseases and Blindness.²⁶ Within this one general category there are included numerous patterns of intellectual, perceptual, conceptual, linguistic, sensory, motor, and behavioral difficulties. This diagnosis has its basis in the demonstration of one or several of these patterns.

There has been considerable opposition to this term, both from within and outside the medical profession, because of the very large variety of symptoms and signs which may lead to its use as a wastebasket sort of label.^{79,85} However, in its generality and stress on *dysfunction*, rather than on *disease*, this designation has the great advantage of indicating the need for special help, and still avoiding the branding of a child as "organically damaged."⁶ The term may be properly used for some children whose dysfunctions stem from largely social or psychogenic difficulties, as well as for those with borderline organic disorders of the brain.

When appropriately used, the term *minimal brain dysfunction* carries the implication of a relatively minor, hidden type of difficulty.²⁸ Unfortunately, it has been frequently confused with the older terms, *minimal brain injury* and *minimal brain damage*, which were formerly applied to the same types of problems. In contrast to the older terms, this newer designation implies flexibility, remediability, and a generally favorable prognosis.^{26,28}

Cruikshank noted a possible hazard of these labels: "... the use of the word 'minimal' frequently serves to minimize the problem in the minds of parents or to place it on a level of less seriousness than it deserves. In reality these children present the most complicated of all learning and adjustment problems . . . There is nothing minimal about any brain dysfunction."³⁷ It is also important to realize that any misdiagnosis or misunderstanding of this type of problem can have potentially serious long-term implications for the child and his family.^{40,41,42}

Any form of deviant maturation in children has

a strong tendency to produce anxiety.²¹ Common defensive reactions against such anxiety include (1) attention-getting, hostile or aggressive behavior, (2) tics and other compulsive habits, (3) apathy, disinterest, daydreaming, withdrawal from social activities, bizarre attitudes, and autistic trends, (4) regressive phenomena such as recurrence of enuresis, (5) physical complaints, hypochondriasis, and somatization reactions.^{53,68,117,119,120} Any of these reactions may be the first indication for the parents to consult a physician about a learning problem.

However minimal, any grade of cerebral dysfunction is accompanied by some degree of ego weakness.¹¹ Many terms have been used to describe the deficiency in ego development or identity formation which generally occurs in children with learning problems: inferiority complex,¹⁰¹ pseudoneurosis,⁸⁰ impaired self-esteem, poor self-image, self-hatred,¹¹³ and others. An understanding of the nature of this ego weakness is essential for proper management of the entire learning disability.

Hyperkinetic Behavioral Syndromes

One of the most common difficulties in management is the hyperkinetic behavior syndrome, also called impulse control deficit, Strauss syndrome, and other terms. In this condition various degrees and combinations of motor restlessness, impulsivity, distractibility, short attention span, emotional lability, and outbursts of temper may occur.^{116,122}

This type of behavior is often erroneously regarded as entirely psychogenic—hence, the recent designation *pseudoneurosis*.⁸⁰ However, in most instances, hyperkinetic behavior probably reflects an imbalance in the functional relationships of the reticular formation of the brain stem with the limbic system and neocortex.^{105,127} Correction of this anatomical-functional imbalance probably is the basis for the frequently observed paradoxical quieting and stabilizing effects of stimulant drugs.

Psychiatric Studies

Most children with learning disorders show indications of emotional or behavioral reactions, both as a result and a complication of their failure to learn. In some instances these reactions are so severe that the entire complex problem may be wrongly considered to be primarily psychogenic. Conversely, in some children the emotional reac-

tions are kept well concealed. In general, the longer the delay in diagnosis and effective help for a milder learning disorder, the greater the effect on a child's personality.⁵⁷

Rabinovitch and coworkers¹⁰⁹ contrasted the differences in emotional reactions and therapeutic needs of children with different types of reading disability. Those cases classified as "primary reading retardation," based on a hidden neurologic deficit, show prominent anxiety and guilt about the reading incapacity itself. Children with "secondary reading retardation," based on exogenous factors, tend to show a wider range of emotional and behavioral problems, with their major anxieties centered on other problems and not mainly around school adjustment.

Failure to recognize the possible neurological background of a learning problem in a child with minimal brain dysfunction may lead to more serious psychic trauma, to which the child is already predisposed because of a coexistent lowered emotional threshold.¹¹ Another serious problem is the common inability of parents to recognize and secure early help for the secondary emotional symptoms which follow upon school failure and social rejection. Often, the child's most urgent need is to have a suitable opportunity to achieve some degree of real academic success as soon as possible.^{97,98,131}

In certain children, passive-aggressive behavior patterns present one of the most serious and treatment-resistant problems leading to underachievement, despite average or superior intellectual endowment. These patterns generally reflect difficulties arising from complexities of interaction between the child and his parent, often aggravated by pressures at school.^{85,110} In some cases other complex problems in family psychopathology operate as causative or complicating factors in learning disorders.^{45,87} Failure of a specific remedial educational program may result from a severe family problem, in which one parent, usually the father, is found to be a borderline psychotic whose social stability is preserved by the family's actions to maintain the status quo; the child's refractoriness to treatment is tied to his role in the family—a pseudostupid or infantile subidentity.⁹⁵

Early psychoanalytic writers stressed the importance of psychogenic factors in some cases of reading disability, implicating early traumatic incidents with later anxiety and guilt over unconscious scopophilic-coprophagic-phallographic phantasies,

regressive gratification of genital impulses, and ambivalence about compulsive exhibitionistic-voyeuristic activity.^{3,18,128,130} Even as late as 1960 Anthony stated, "In general, most psychoanalytic authors agree that a regression to a sexualized and aggressivized mode of energy is characteristic of learning problems."⁵

While formulations in such terms may not be generally useful, there is no question that optimal levels of sensory and perceptual stimulation in very young children have great importance for the future development of language skills, problem solving, and other cognitive functions. Early distortions in the child's personality development related to maternal deprivation and other disturbed family relationships often lead to serious impairment in future learning abilities, as well as behavior disorders, psychopathic traits, and psychophysiologic derangements.²³

Such factors influence every therapeutic program for children who have had any appreciable degree of early personal deprivation, whether determined mainly by cultural and economic factors or by intrafamilial problems. Special difficulties presented by linguistic and motivational barriers to academic achievement in culturally deprived children, even in the earliest school years, also reflect attitudes which are likely to influence psychotherapy and other phases of medical treatment.¹⁰²

Diagnosis: the Interdisciplinary Team Approach

There is no single neurological pattern which is diagnostic of a learning disorder. Indeed, a learning disorder of any type, from a specific developmental dyslexia to a severe global mental retardation, may occur without any clear-cut abnormalities in the standard neurological examination.

An accurate diagnostic formulation of learning disorders requires consideration of multiple factors—social, educational, pediatric, psychiatric, neurologic, psychologic, and linguistic. It is essential that any physician consulted about a learning problem understand, first, the limitations of his own abilities and, second, the potential value of securing other help, both in diagnosis and therapy, from those in other medical specialties and in the cooperating professions.

An interdisciplinary group for comprehensive diagnostic study, and for the formulation and carrying out of a treatment program, may include various specialists in family practice, pediatrics,

psychiatry, neurology, ophthalmology, otolaryngology, psychology, education, speech pathology and linguistics, social service, occupational therapy, physical therapy, and nursing. A "minimal" interdisciplinary team for learning and language disorders would consist of a physician, a psychologist, a speech pathologist and a teacher.⁵¹

As a member of an interdisciplinary team, a physician must set aside, to some extent, his traditional role as an absolute authority on diagnosis and treatment. He must recognize and be able to make proper use of the unique training and frequently superior skills of the other members of the team.^{133,136}

Modern psychological testing, using a variety of standardized tests, provides the most refined diagnostic study of many of the highest cerebral functions, usually far beyond the range of the most extended study by a neurologist or psychiatrist. Similarly, the special evaluations carried out by a speech pathologist and an educational consultant provide detailed assessments of other complex functions of the nervous system. The examinations made by these specialists, who often overlap in their interests and skills, are essential to the diagnostic study and remedial planning for a child with a learning disorder.²⁶

Treatment: Psychotherapy

All non-educational types of treatment for learning disabilities are merely adjunctive or auxiliary to a remedial educational program, which is designed to help the specific cognitive deficits of an individual child. Psychotherapy is not a specific form of treatment for learning problems, except for those relatively uncommon cases in which the learning difficulties appear to be largely psychogenic.⁸²

A careful explanation about the nature of a child's learning problem usually has great value to the child and to his parents and often to his teacher, as well.⁶⁰ Any indications of limited grasp due to severe anxiety, denial mechanisms, and other problem attitudes should suggest the need to provide further guidance or other psychotherapy for the child and his family. More extensive psychiatric evaluation is also indicated whenever a child's behavioral difficulties and symptoms continue despite educational and other environmental help.^{56,102}

Psychotherapeutic help in many cases may be appropriately limited to practical counseling or

guidance for the parents. In most instances parents should be advised to provide an orderly, carefully planned, predictable schedule of home activities in a setting of consistently firm and fair discipline with definite limits of permissiveness, accompanied by kindness, understanding, helpfulness, and encouragement.

Whenever necessary, parents should have help in developing general guidelines and in planning the details of physical activities, recreation, and periods of rest. Usually, the physician should confer with the child's remedial teacher, school psychologist and other consultants before making specific recommendations to the parents about educational matters, such as advice about securing home tutoring or referral to a special school or clinic.

The preliminary planning should consider every available type of standard therapy which might improve the child's total functioning. In most cases, any indicated psychotherapy, drugs, and physical exercise programs can be advantageously used in combination during any phase of remedial education. More rarely, some preliminary period of psychiatric intervention (psychotherapy or drug therapy or both) may be necessary before a child can participate adequately in a remedial educational program.⁵²

Ideally, each portion of a "total push" program enhances the efficacy of all of the other means which are being used simultaneously. However, in some cases, too full a schedule may exhaust the energies of children and their parents. No form of treatment, however valuable, should be allowed to take away energy which is more urgently needed for other activities.⁷⁴ A hierarchy of treatment needs and values must be established and periodically reviewed in every case.

In some older children and adolescents more time and attention may appropriately be devoted to some form of direct psychotherapy with the child himself. But in every case the parents should also be involved in varying degrees. Other briefer supportive and interpretive forms of therapy may be considered in many instances. For some families a conjoint approach may be useful.^{48,102}

Most children with learning problems and their families derive considerable emotional support from the continuing interest and availability of their family physician. This continuing relationship provides for prompt help, whenever needed, over an extended period.⁵²

Motor and Perceptual-Motor Therapies

Several programs which emphasize training in body control and visual perception are currently in wide use for children with learning disorders. The methods advocated by Kephart, Getman, and Delacato use a number of similar techniques but with wide differences in theoretical bases.

Kephart's method for developing basic "motor generalization" is supposed to promote perceptual accuracy.^{72,73} Getman believes that deficiencies in various visual functions are the basis of learning difficulties; he combines visual training and general motor training.⁵⁵

The Doman-Delacato group believe that children with learning disorders lack "neurological organization." Their training methods aim at a patterned recapitulation of the phylogenetic-ontogenetic stages of locomotor development. They emphasize the use of measures to establish complete unilaterality of motor dominance for eye, hand, and foot, in the belief that these will accelerate and stabilize the localization of language functions in the dominant cerebral hemisphere.⁵⁰

All of these methods may have some value to some children with impaired motor and visual motor skills. The possibility that certain features of these methods may have particular value in some cases requires careful study. However, there is no clear evidence that any of these techniques has any specific educational value for the cognitive functions of children with learning disorders.

There has been considerable concern over the claims of the Doman-Delacato supporters for their theories and techniques which are not consistent with accepted neurological principles.^{50,138} Such a complex regimen may be potentially harmful to an individual child and his family when indiscriminately applied, especially in the place of more specific remedial educational techniques.¹³⁸ In 1968 twelve major health organizations in the United States of America and Canada concurred in a statement opposing the Doman-Delacato method.⁹²

In addition to the Getman program, many other orthoptic and optometric treatments are being used for children with learning disorders.⁶⁴ While eye muscle imbalance, convergence difficulties and refractive errors may contribute to learning problems, eye conditions are not generally regarded as the major etiologic factors.

That various unorthodox and faddist programs for children with learning disorders have had such rapid growth and wide use reflects a possible seri-

ous deficiency within the medical profession. Parents and educators have felt a critical need for more specific techniques and active help for children with learning and language disabilities. The longstanding tendency to isolationism of the medical profession and consequent barriers to freer communication with other concerned professions must be quickly broken down.^{24,138}

Physicians have a serious responsibility to inform and advise parents and educators about the rationale—the possible value and also the potential harmfulness — of any medically based program proposed for treatment of children with learning disorders, either within or outside the classroom. The relevance of any treatment to each child's specific problems should always be the primary consideration.⁹⁰

Early motor disabilities, even when mild and borderline, often lead to exclusion from play activities of peer groups, giving the child insufficient opportunities and motivation to practice motor skills, and a progressive aggravation of the child's basic deviations from the average motor development for his age.⁷⁴

Children with such borderline motor and visuo-motor handicaps may derive considerable help from a carefully planned remedial program designed to improve motor skills, body image awareness, right-left discrimination, and hand-eye interactions.^{34,35,37}

Many school systems still do not provide formal physical education programs until the level of junior high school or beyond. And most physical education programs chiefly provide an opportunity for the practice and improvement of motor skills already developed outside of school. Fortunately, some school systems are providing more ideal individualized remedial physical educational programs for children with borderline motor handicaps which complicate other learning problems. Physical therapists, occupational therapists, and physical educators with special interest and training can give considerable individual help to children with such difficulties. Physicians should have greater awareness of the general need for improved programs in physical education.³⁵

Cerebral Dominance

Treatments such as the Doman-Delacato method and some optometric programs which emphasize motor activities and other measures, such as eye occlusion, designed to influence cerebral domi-

nance, have no sound theoretical basis for the general treatment of learning disorders.^{97,138}

The entire problem of cerebral dominance is far more complex than previously believed. It is now recognized that the left cerebral hemisphere is dominant for language functions in many, probably a majority, of left-handed persons as well as in right-handers.^{91,100,129,141,142}

While anomalous handedness and mixed or confused eye-hand preference frequently occur in children with learning disorders, these do not have any cause-effect relationship.^{9,141} It is well known that similar patterns of confused or mixed motor laterality occur in the general populations with great frequency.¹³⁸

Handedness exists in many gradations; estimates of the incidence of left handedness vary from 1 percent to 30 percent in different studies, using different criteria and examination techniques.⁶⁵

Cerebral laterality for handedness and language are not directly linked, and one does not determine the other.⁹¹ Exercises and eye treatments which are designed to change laterality of motor skills cannot be expected to provide an effective basis for the specific treatment of a child with a complicated deficit in perceptual and other cognitive abilities.

Drug Therapy

Drugs have only relatively limited usefulness in the broad field of learning disorders.⁴⁹ However, in certain cases the proper use of a specific medication can be of great value in controlling behavioral symptoms which interfere with learning.^{43,46}

The cerebral stimulant drugs have been shown to have a paradoxical calming effect on hyperkinetic behavior. Either dextro-amphetamine (Dexedrine®) or methylphenidate (Ritalin®) may be effective when used in proper doses. These drugs may also be helpful for some children who have a short attention span or difficulty in concentration but are not otherwise hyperkinetic. Deanol (Deaner®) is a more controversial stimulant which may be of value in some cases.^{96,137}

Barbiturates and mild tranquilizers of the propanediol series, such as meprobamate (Miltown®), have generally less value in these problems and may actually have an undesirable paradoxical stimulant effect.

In some more severe forms of hyperactivity, especially when accompanied by more bizarre, negativistic, aggressive, schizoid or autistic behavior,

one of the major tranquilizers of the phenothiazine series may be useful. Here the choice generally lies between a more sedative agent such as chlorpromazine (Thorazine®) and thioridazine (Mellaril®) and a more stimulant drug such as trifluoperazine (Stelazine®) or fluphenazine (Prolixin®, Permitil®).

Other drugs which have been advocated for hyperkinetic behavior disorders include diphenylhydantoin sodium (Dilantin®), diphenhydramine (Benadryl®), hydroxyzine (Atarax®, Vistaril®), chlordiazepoxide (Librium®), and diazepam (Valium®). Anticonvulsants, such as diphenylhydantoin (Dilantin Sodium®) and primidone (Mysoline®), may best be reserved for use when a subclinical convulsive disorder is suspected.

In younger children with enuresis the tricyclic (iminodibenzyl) antidepressants, such as imipramine (Tofranil®) and nortriptyline (Aventyl®) are frequently quite valuable, both in providing fairly prompt bladder control and in helping classroom behavior. Older children and adolescents who have depressive trends also may be helped by tricyclic agents.

The dosage of any of these drugs should be individually adjusted, usually starting with small doses and increasing as rapidly as possible to the optimal effective level. Adequate arrangements should be made in every case to assure appropriate observations and medical supervision. Physicians may advantageously use the help of teachers and school nurses, both in administering a midday dose of medication and in observing the effects of a drug on the child's behavior in a variety of situations at school.^{83,135}

Many physicians disapprove the use of psychotropic medications for behavior disorders, on the ground that the prescription of drugs might be misinterpreted by parents or teachers and brand the child as "organically damaged." Others, especially psychiatrists, have viewed drugs as potentially anti-psychotherapeutic.

Drugs obviously cannot take the place of necessary remedial education, psychotherapy or environmental changes. However, appropriate drug therapy may facilitate any needed psychotherapy or special educational program. Postponement or refusal of a trial of indicated medication in behavioral syndromes complicating learning disorders can be an unwarranted barrier to prompt relief of symptoms which block learning.

Conclusion

Through his broad knowledge of higher cerebral functions and their complex relationships with general physical and mental health, the physician is in the best position to help parents understand their child's learning problem and to secure their cooperation in arranging for any necessary remediation. The physician is also the appropriate person to provide the general public, including legislators and school administrators, with sound information on the medical aspects of learning problems.²⁹

The physician has a major responsibility to provide the leadership in the development of team programs, to help integrate diagnostic and therapeutic procedures, and to work vigorously toward providing earlier and more complete help for children with learning disorders.^{42,52} It is clear that if the physician cannot play a leading role, these problems will be dealt with by those less competent to do so.⁹⁰

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ALPHA-TOCOPHEROL TO FORFEND THROMBOSIS

"About 19 years ago, a young man at our institution did some work on blood coagulation. He showed that alpha-tocopherol in the presence of calcium exerts an antithrombic effect. In the last 18 years, I have been using this routinely in all patients in whom I've done major surgical procedures. And in the 18 years that I've been using this routinely and immediately after operation, I've had one case of pulmonary embolism. I thought this was the one failure. But autopsy showed that the man's embolus came from his atrium, and not from his peripheral arterial system. He had it at the time we operated on him. So I think that this is a real worthwhile drug. The advantage of it is that although it decreases the thrombic activity, it doesn't increase the bleeding tendency. We use 100 international units, three times a day, given parenterally first and then by mouth."

—ALTON OCHSNER, M.D., New Orleans

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Ocular Findings in Several Metabolic Diseases

WARREN A. WILSON, M.D., *Los Angeles*

■ *Changes in ocular findings have been noted in association with several metabolic diseases.*

In homocystinuria the crystalline lens in the majority of cases is subluxated inferiorly, while in Marfan's syndrome the dislocation was upward.

In cystinosis, slit-lamp examination reveals numerous gold crystal-like cystine deposits in both the cornea and bulbar conjunctiva.

Patients with galactosemia have cataracts of the "oil drop" type, which usually can be seen with an ophthalmoscope even though the opacity is not dense.

Eight patients with Lowe's syndrome who were observed had cataracts, and four of them had severe glaucoma.

Three of five patients with glycogen storage disease Type I had yellowish deposits in the macular and paramacular areas, thought to be due to hypercholesterolemia.

MANY PHYSICIANS do not realize the extent to which ophthalmologic findings are associated with defects of metabolism. Although these conditions are rare, there is always a good possibility that an ophthalmologist will encounter one or more in the course of his practice. The entire scope cannot be covered here, but several metabolic diseases and syndromes studied by the author will be discussed. The entities to be considered are homocystinuria, Marfan's syndrome, cystinosis, galactosemia, Lowe's syndrome, and glycogen storage disease, Type I.

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Homocystinuria

Homocystinuria,¹ a disorder of amino acid metabolism, was first described in 1962. It begins in infancy. Patients have a malar flush, fine hair and congenital anomalies. Mental retardation and dislocation of the crystalline lenses are the chief findings. Many of the patients die, due to thrombosis of major vessels. The physical characteristics of these patients resemble those seen in Marfan's syndrome, a different metabolic problem in which there is cardiac disease but no thrombosis of the vessels. The diagnosis of homocystinuria is made by finding homocystine in the urine. In this disease the subluxation of the crystalline lenses is downward; in Marfan's syndrome, it is upward.

Cystinosis

Cystinosis,² or Lignac-deToni-Fanconi syndrome, is a systemic disease of unknown cause. The generalized amino-aciduria and renal glycosuria associated with this condition are clues to the diagnosis. Rickets is a consistent finding and the patients have been sometimes called nephritic dwarfs. Death frequently occurs during the first ten years of life due to renal insufficiency. Depositions of cystine crystals occur in various tissues. These crystals are easily visible with the slit-lamp in the stroma of the cornea, appearing as myriads of fine gold flakes. They probably account for the photophobia which is a common complaint. The crystals are also present in the conjunctiva. By ophthalmoscopic examination alone, the cornea may be completely clear, and the diagnosis thus may be missed. Cystinosis should not be confused with cystinuria.³ Cystinuria is inherited as a recessive disease which is characterized by the frequent formation of cystine urinary calculi as the most important clinical finding.

Galactosemia

Galactosemia⁴ is an inborn error of carbohydrate metabolism. There is a deficit in the activity of a specific enzyme, galactose-1-phosphate uridyl transferase. Infants with galactosemia appear normal at birth and do well until milk feedings are begun; then certain symptoms such as fever, vomiting, inability to gain weight and, at times, diarrhea occur. Jaundice and hepatomegaly are consistently found, and splenomegaly occasionally. Ascites may occur. It is important to diagnose the condition at this stage because most of the symptoms and findings can be reversed by prescription of a lactose-free diet. If untreated, the surviving infants develop cataractous changes and mental retardation. The diagnosis is suspected on clinical grounds and strengthened by the finding of a reducing substance (galactose) in the urine. The usual test using Benedict's solution produces a positive reaction, but there is a negative reaction when glucose oxidase is used. The diagnosis is now confirmed by the absence of transferase enzyme activity in red cells. The enzyme activity is nil or almost nil in the hemolysates of patients with galactosemia, and the activity is reduced in carriers.^{5,6}

The evolution of the genetics of galactosemia took years of study before Kirkman and Bynum⁵



Figure 1.—Galactosemic cataract with surgical coloboma.

and Donnell, et al⁶ established that the inheritance of the disease is as an autosomal recessive. It is extremely important in genetic counseling to warn the parents that subsequent babies may have the same disease. The risk is one out of four in each future pregnancy.

In the last 20 years, 45 patients with galactosemia have been examined and treated at the Children's Hospital of Los Angeles. The author has had the privilege of examining the eyes of all of these patients and of following them periodically. Cataract is the main eye defect associated with galactosemia; it was present in 42 percent of the patients. It is suspected that the changes in the crystalline lens are due to accumulation of galactitol, an end-product of an alternate galactose pathway.⁷ These cataracts have often been referred to as the "oil drop" type (Figure 1) because of their appearance upon examination with the ophthalmoscope. Biomicroscopic examination reveals cloudy changes in the embryonic and fetal nuclei and there may be fine radiations extending out in the posterior cortex. About two-thirds of the central area is usually involved. The peripheral cortex may remain quite clear. Interestingly, over the years, operation for removal of galactose cataracts has been done in very few cases. The author reported performing optical iridectomy on one of our first patients.⁸ In this case, the diagnosis was not made until the infant was seven months of age, and the cataracts had much more time to develop.

Sometimes there are no opacities whatsoever in the crystalline lens. In most of the cases diagnosed during the first month of life the opacities have been minimal. It has been reported that galactose cataracts will completely resolve with dietary treatment, but in our experience some minimal opacity



Figure 2.—Lowe's syndrome. Corneas cloudy from glaucoma. Cataracts present.

remains in the crystalline lens even though there is regression of the cataract.

It is stated in the literature that cataracts do not occur in patients less than one month of age. However, we had one patient who was diagnosed as having galactosemia at two and a half weeks of age and the opacities were quite advanced and easily seen on ophthalmoscopic examination. The lens changes almost entirely regressed in this case after the patient began receiving a prescribed diet.

Opacities of any kind in the crystalline lens may cause some impairment of vision. In the patients we have observed over a period of many years, it has been found that the eyes do not always have 20/20 acuity, but useful vision is usually present.

Lowe's Syndrome

The oculo-cerebral-renal syndrome of Lowe⁹ is a relatively new disease, first described in 1952. This is a congenital and inherited condition manifested by defects of the nervous system, the eyes and the kidneys. Laboratory tests disclose proteinuria and hyperaminoaciduria.

Eight cases seen at the Children's Hospital were reported in 1963.¹⁰ All the patients were male, were short of stature, were severely mentally retarded and had cataracts. Four had congenital glaucoma as well (Figure 2). Seven of the eight had bilateral cryptorchidism.

The cataracts varied from partial to total involvement of the crystalline lens. The four with glaucoma perhaps should have been listed as having hydrophthalmos, for the condition was present at birth and was characterized by pro-

nounced edema of the cornea and by high intraocular pressure as determined by tonometer with the patient under anesthesia. Operation for glaucoma in these cases was basically limited to iridencleisis because the corneas were not clear enough for the performance of goniotomy. In a few cases, goniotomy was performed as a secondary procedure when the corneas were clearer. Complete control of the intraocular pressure was not satisfactory, and the cataract operation was only partially successful. Because of the mental retardation, it was impossible to determine visual acuity in these patients, nor was it possible to tell whether or not they were deaf. The cataract operation was either linear extraction or aspiration. All patients had some posterior capsular remnants which precluded an adequate view of the fundus.

The genetic aspect of this disease is extremely interesting. The parents, siblings and grandparents of all of the patients we observed were given a thorough ocular examination. On slit-lamp examination three mothers and one maternal grandmother were found to have partial cataracts. Four mothers had numerous punctate opacities throughout the cortex of the crystalline lens of both eyes. The opacities often had the appearance of snowflakes. Similar changes were present in the crystalline lens in two maternal grandmothers, one maternal aunt and three female children. Based on pedigrees and the fact that all patients are males, Lowe's syndrome is generally considered a sex-linked disorder. The ocular findings described in mothers and female relatives are manifestations of the heterozygous state.

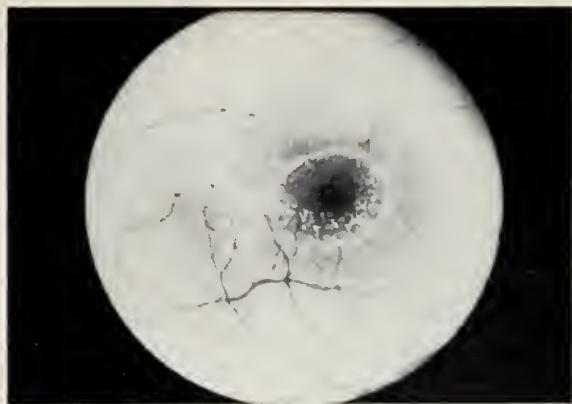


Figure 3.—Macula in glycogen storage disease.

Glycogen Storage Disease

Glycogen storage disease Type I, sometimes referred to as Von Gierke's disease, is a hereditary metabolic disorder manifested by low or absent activity of the enzyme glucose-6-phosphatase in the liver, kidney and small intestine. There is an accumulation of glycogen in these tissues—hence the term “glycogen storage disease.” Clinically, the disease is characterized by short stature, massive hepatomegaly, hypoglycemia, lactic acidosis and hyperlipidemia.

Five cases of glycogen storage disease were studied in considerable detail, including complete ocular examination.¹¹ Three of five patients had multiple bilaterally symmetrical, yellowish, non-elevated discrete paramacular lesions (Figure 3). The media were clear on biomicroscopic examination. The blood vessels and optic discs appeared normal and no lesions were noted in the periphery of the fundus. Changes were striking in one case, less so in the others. There was no visual impairment and no evidence of other ocular disease in any of these patients. The patients had elevation of blood phospholipids, triglycerides, cholesterol and total lipids. The patient with the greatest ocular involvement had the highest levels.

Similar yellowish spots in the macular and paramacular areas have been observed in a number of adults and an occasional older child who do not have glycogen storage disease. In these cases, the blood cholesterol has been decidedly elevated, usually in the 400-500 mg per 100 ml range. In our series of glycogen storage disease patients, only three had elevated cholesterol levels (542, 518 and 315 mg per 100 ml). Cholesterol level were within normal limits in the other two patients. To date, we have no histopathological studies to verify what the tissue changes in the retina may be. Because of the high cholesterol content in the blood and in light of the fact that the yellow spots have been seen also in adults without Von Gierke's disease, it is thought that the changes are due to cholesterol crystals or deposits. A low cholesterol diet in adults who do not have Von Gierke's disease has been reported as reversing the ocular findings. However, in Von Gierke's disease, the cholesterol and other lipids continue to be higher than normal despite low dietary intake.

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CASE REPORTS

Hypogonadotrophic Hypogonadism in Hemochromatosis

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HYPOGONADISM, one of the classic manifestations of hemochromatosis, was studied in two patients with this disorder. The clinical and histological findings in the two patients were correlated with measurements of gonadal and gonadotrophic hormones.

Reports of Cases

Case 1. The patient was a 32-year-old white man who had diffuse skin pigmentation since age 12. His pubic, facial, and axillary hair had always been sparse. His testes had not grown since age 11, but he believed his libido had developed normally. Cardiac manifestations which led to the admission of this patient to hospital have been reported elsewhere.¹

At admission it was observed that diffuse pigmentation of the skin gave it a slate-grey appearance and it was smooth and hairless. The patient was 76½ inches tall, his arm span was 79¼ inches, crown-to-pubis segment 36½ inches, and pubis-to-floor segment 40 inches. The escutcheon

was that of females. The testes were soft and each measured 1.8 cm in maximum diameter, the penis was small and the prostate gland not palpable. Gynecomastia was absent. The liver edge was felt 8 cm below the right costal margin.

The serum iron level was 270 µg per 100 ml and the unsaturated iron-binding capacity was less than 50 µg per 100 ml. Results of a standard oral glucose tolerance test were as follows: fasting blood glucose, 104 mg per 100 ml; one-hour, 218 mg; two-hour, 264 mg; three-hour, 304 mg; and four-hour, 134 mg per 100 ml. Liver function studies showed no abnormality. Urinary excretion of 17-ketogenic and 17-ketosteroids was within normal limits, as was the response to a standard oral metapyrone test. Results of thyroid function tests were normal. The plasma testosterone level² was 0.088 µg per 100 ml (normal 0.3 to 1.1). The levels of plasma luteinizing hormone (LH)³ and of plasma follicle stimulating (FSH) hormone⁴ were each less than 5 milliInternational Units (mIU) per ml (normal 5 to 30).

Biopsy specimens of liver, skin and heart revealed evidence of hemochromatosis. Biopsy sections of a testis (Figure 1) revealed a prepubescent appearance. The seminiferous tubules contained numerous Sertoli cells with only occasional primordial sex cells. An occasional tubule was sclerotic. Iron deposition was noted in some of the Sertoli cells, but not in the scanty stromal fibroblasts. The patient has been treated with weekly phlebotomy, insertion of an epicardial synchronous pacemaker,¹ and fluoxymesterone, 10 mg daily.

Case 2. A 66-year-old father of two daughters, aged 33 and 39 years, had hemochromatosis diagnosed and confirmed by liver biopsy at age 54 in 1954. Insulin-dependent diabetes mellitus was also found then. Since 1954, the patient had been treated with multiple phlebotomy. Liver biopsy sections in 1962 revealed disappearance of abnormal iron staining.

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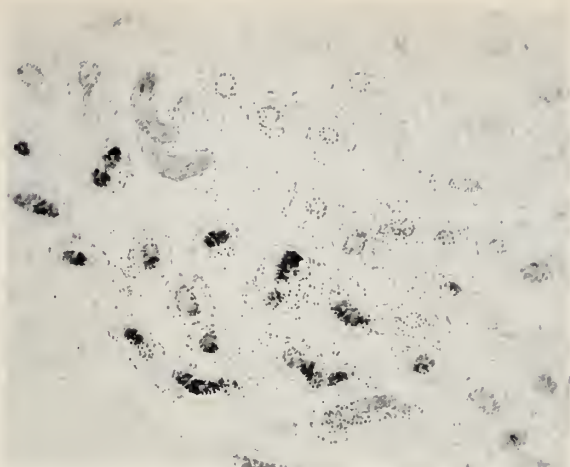


Figure 1.—Section of testis (Case 1). There is immaturity of the seminiferous tubules with an occasional sclerosed tubule, loose stroma, and absence of Leydig cells. Iron deposits are present only in the Sertoli cells. (Gomori's iron reaction, 100X).

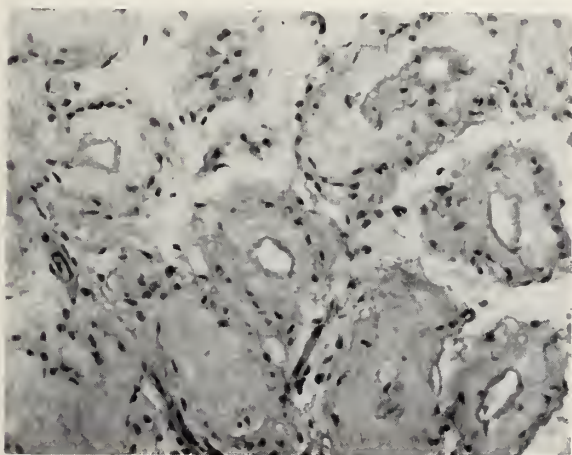


Figure 2.—Section of testis (Case 2). There is pronounced thickening of the seminiferous tubules and absence of spermatogenesis. The Leydig cells are scanty and atrophic. No iron deposits are seen. (Gomori's iron reaction, 300X).

In 1966, the patient had fine wrinkling of the forehead, minimal bitemporal hair recession, and scanty axillary and pubic hair. His testes measured 3 cm in greatest diameter and were soft. The penis was 7 cm long, the prostate gland of normal size. The liver edge was palpable 3 cm below the right costal margin.

Liver function studies were within normal range. The fasting glucose level was 192 mg per 100 ml. Results of thyroid function tests were normal. Urinary excretion of 17-ketogenic and 17-ketosteroids was normal, as was the response to a standard oral metapyrone test. The plasma testosterone level was

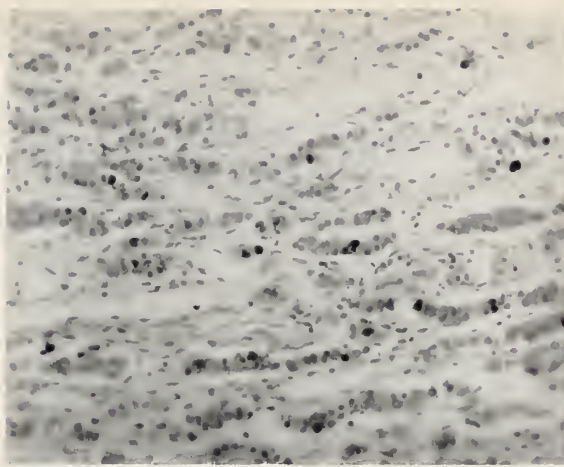


Figure 3.—Section of pituitary gland in Case 2. Numerous iron deposits are seen in all cell types, especially the basophils. (Gomori's iron reaction, 200X).

0.082 μ g per 100 ml. Plasma LH level was low (< 4 mIU per ml) as was plasma FSH content (< 3 mIU per ml).*

Biopsy sections of the testes revealed moderate sclerosis of the seminiferous tubules, with spermatogenesis absent (Figure 2). The interstitial cells were sparse and atrophic. No iron deposits were present.

A year after the above studies were performed, the patient died of a primary hepatoma. At autopsy, both testes were atrophic, and no iron deposition was present. There was, however, extensive iron deposition in the pituitary gland, especially involving the basophils but also other cell types (Figure 3). Extensive fibrosis and iron deposition were also present in the pancreas. No abnormal iron deposition was seen in the liver.

Discussion

The findings in both patients are consistent with the diagnosis of hypogonadotrophic hypogonadism.^{5,7} The case of the younger patient is a classical example of hypogonadism due to pubertal pituitary gonadotrophin failure. He had eunuchoidal features, clinical and laboratory evidence of androgen deficiency, and testicular histology characteristic of this disorder. He also had low levels of plasma LH and FSH fitting the clinical syndrome of "isolated" hypogonadotrophic hypogonadism recently reported by Hornichter et al.⁸ This patient resembled one reported by Althausen and Kerr⁹ in whom hypogonadism also antedated puberty and

*The FSH and LH assays were performed by Albert F. Parlow, Ph.D., Harbor General Hospital, Torrance.

was believed by the authors to be due to a disturbance of pituitary function secondary to iron deposition. Although symptoms develop before age 30 in only 4 percent of patients with hemochromatosis,¹⁰ pituitary gonadotrophin insufficiency was believed to be the cause of hypogonadism in another subject with juvenile onset hemochromatosis.¹¹

The older patient of the two reported upon herein had the more usual, later onset of gonadal failure. Testicular histology resembled that of a patient with hemochromatosis classified by Albert¹² as typical of adult onset hypogonadotrophic hypogonadism. Also the low plasma FSH and LH together with the low PT are consistent with the diagnosis of hypogonadotrophic hypogonadism and provide evidence against primary testicular failure, in which increased gonadotrophins would be expected.^{7,13}

Iron deposition in both the pituitary gland and testes is common in hemochromatosis.¹⁴ Although hypogonadism occurs in some patients with hepatic insufficiency, it is unlikely that testicular failure in the two cases presented can be attributable to liver disease. Hypogonadism, when it occurs in hepatic disease, is usually associated with advanced clinical¹⁵ and morphological¹⁶ stages of hepatic decompensation. In both patients, hepatic function studies were normal at the time of the tests to determine endocrine function.

Until recently, complete pituitary insufficiency had not been documented in hemochromatosis except in rare reports of massive or focal necrosis of this gland.¹⁷ Pituitary iron deposition in the two cases presented here appears to have selectively impaired gonadotrophin function. A recent report, however, demonstrates that deficiencies of other anterior pituitary hormones may also occur in this disease.¹⁸ The present study indicates that impaired FSH secretion as well as impaired LH secretion contributes to the hypogonadism of hemochromatosis.

Summary

Hypogonadism, one of the classic manifestations of hemochromatosis, was studied in two patients with this disorder. The clinical and histological findings were correlated with measurements of gonadal and of gonadotrophic function. Hypogonadotrophic hypogonadism was found in both patients.

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Polymyalgia Rheumatica and Associated Arteritis: A Review

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POLYMYALGIA RHEUMATICA is a syndrome which has been described during the past 15 years, mostly by the English and Scandinavians, but articles have appeared in the American literature with increasing frequency since the first case report in 1963.¹

It affects middle-aged and elderly persons, infrequently those under the age of 50 years, with women more often afflicted than men. The chief complaints consist of pain and stiffness of shoulder and pelvic girdles, with constitutional symptoms and decidedly accelerated erythrocyte sedimentation rate (ESR) but without significant objective findings or x-ray changes. Generally, the disease runs a self-limited course, with complete recovery occurring spontaneously after several years, but the course may be shortened and morbidity decreased by treatment with corticosteroids.

History

Retrospectively, this syndrome was probably first described by a British physician named Bruce in 1888² who referred to "senile rheumatic gout" with severe pains followed by complete recovery. Then no further recognizable reports appeared until 1945 when Meulengracht³ described "humero-scapular periartrosis" with fever, weight loss and elevated ESR. In that same year Holst and Johansen⁴ spoke of "peri-extraarticular rheumatism" occurring in elderly women and associated with low-grade fever and accelerated ESR. Kersley (1951)⁵ described "myalgic syndromes of the

aged with systemic reaction" as severe, widespread muscle pain and tenderness of the scapular and thigh regions, with accelerated ESR but without arthritis. Bagratuni (1956)⁶ discussed "anarthritic rheumatoid disease," characterized by generalized muscle aches and stiffness, especially in the shoulders, neck and back, with fever, weight loss, anemia, malaise, anorexia, accelerated sedimentation rate, absence of arthritic changes roentgenographically and an excellent prognosis. Barber (1957)⁷ described a myalgic syndrome with constitutional effects in 12 patients between 46 and 68 years old, followed for up to seven years, with findings similar to those above, and with a good prognosis. He called this syndrome "polymyalgia rheumatica."

Etiology

The cause of this condition is unknown, but during the past eight years giant cell cranial arteritis has been implicated as the underlying histological lesion by various authors.

Porsman⁸ in 1951 was the first observer to associate multiple myalgic pains and aches with temporal arteritis. Paulley and Hughes⁹ believed that the myalgias usually precede arteritis by weeks to years. Following up these clues, they performed temporal artery biopsy on 23 patients with both symptomatic temporal arteritis and polymyalgia rheumatica without obvious artery tenderness and swelling and found 21 to have histologic changes of arteritis. It now seems quite clear that the myalgias and arthralgias of giant cell arteritis which present as temporal arteritis can closely mimic the symptoms of polymyalgia rheumatica, and may definitely antedate the obvious vascular changes.¹⁰ Alestig and Barr,¹¹ on biopsy of asymptomatic

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temporal arteries in ten persons with polymyalgia rheumatica, found giant cell arteritis in seven. They proposed the name "arteritis senilis," based on the ages of the patients, and expressed belief that it is a variant of giant cell arteritis.

Hamrin¹² studied 21 patients with polymyalgia rheumatica, including 12 with asymptomatic temporal arteries, and found giant cell arteritis in 12, of whom six were asymptomatic. Four others showed non-specific inflammatory changes, while the remaining five had normal arteries. It is of interest that in this latter group of five, three had become asymptomatic at the time of biopsy and each of the other two had been symptomatic for less than three months. Hamrin coined the term "polymyalgia arterica" for this condition.

Dixon,¹³ on biopsy of temporal arteries in 28 patients with polymyalgia rheumatica, found ten positive for arteritis. He concluded that these conditions represented a single entity. Wilske and Healey¹⁴ expressed the opinion that polymyalgia rheumatica may either precede or follow symptomatic temporal arteritis. Fessel and Pearson¹⁵ advocated early temporal artery biopsy in all cases of polymyalgia rheumatica in order to rule out the presence of giant cell arteritis and its accompanying danger of sudden blindness from ophthalmic artery involvement when untreated.

A few observers have not accepted the apparent relationship between arteritis and the polymyalgic symptom complex. Bagratuni,¹⁶ who referred to the condition as "anarthritic rheumatoid disease," felt that polymyalgia rheumatica more closely resembles the prerheumatoid features of rheumatoid arthritis. He said that rheumatoid arthritis developed in 2 of his 50 patients, and he also was of the opinion there was no relationship to arteritis. However, he did not perform temporal artery biopsy in any of the patients. Gordon,¹⁷ on the other hand, found no proof that polymyalgia rheumatica was a variant of rheumatoid arthritis and also felt that it was not related to arteritis *per se*. Although his biopsy studies of muscles, synovium and other periarticular structures showed only non-specific infiltration of chronic inflammatory cells, like Bagratuni he did not perform arterial biopsy. Others have found that muscle biopsy is invariably negative, probably because only medium and large sized arteries are affected in giant cell arteritis, whereas such vessels are rarely obtained in routine muscle biopsy specimens.^{11,18,19}

In one instance, reactive depression and my-

algias of the shoulder and pelvic regions developed during isoniazide treatment for urogenital tuberculosis, after 180 grams had been given over a nine-month period.²⁰ This condition was followed by polyneuropathy and it was named pseudo-polymyalgia rheumatica. To date this has been the only case to be reported in which the condition was possibly drug-induced.

Whereas some observers^{7,12,21} consider polymyalgia rheumatica to be a definite disease, others suggest that it is not a specific disease but rather a symptom complex secondary to a number of unassociated diseases²² and may be produced by such trigger factors as excessive fatigue and psychological trauma.²³

Incidence

There is no known racial or geographic distribution. Dixon said that this condition made up 1.3 percent of all cases of rheumatic disease in patients seen in his clinics.¹³ He believed it to be more common than ankylosing spondylitis, as common as gout and, at the age of 70 years, one-half as common as rheumatoid arthritis. At a younger age, it was found in a ratio of 1:12 to rheumatoid arthritis. Regarding the relative incidence as compared with ankylosing spondylitis, the latter condition has been seen much less frequently by the English than by physicians in the United States.²⁴ Many English observers feel that polymyalgia rheumatica is common in elderly people and that the diagnosis is not being entertained.

Symptoms

The old literature described an initial "flu syndrome." Usually the onset of symptoms is quite sudden and patients often remember the exact date and even the hour. The main complaints are pain and stiffness of the shoulder girdles and, somewhat less commonly, the pelvic girdles. Myalgia affects the posterior neck muscles, deltoids, biceps, trapezii, and less frequently the glutei, hamstrings and quadriceps. Pain is worse in the morning and with inactivity. It is also aggravated by motion, especially initially. Swelling is uncommon. There is also less intense pain and stiffness of periarticular structures, including bursae, tendons and sheaths, synovia and capsules.

Constitutional symptoms occur frequently, including fatigue, weight loss, anorexia, sweating, insomnia secondary to pain, fevers lasting for

weeks, and depression. Although fevers are usually of low grade (99 to 100°F), one observer¹⁹ noted fevers up to 103°. Intermittent claudication was noted in one instance²² and pruritus in several others.^{2,12}

Physical Examination

Pertinent findings include fever, slight tenderness of muscles and periarticular areas, absence of muscle atrophy (with one exception reported¹²) and mild limitation of motion which varies with pain and is usually of short duration. Tenderness or nodular swellings or both along the course of cranial arteries is often present. Small, asymptomatic effusions of one or both knees were recently reported by Wilske and Healey¹⁴ in 8 of 18 patients. Murmurs were heard over large arteries in 30 of 52 patients studied.²⁵ Palpable synovial thickening of one or both sternoclavicular joints was observed in 32 of 80 patients.²⁶

Laboratory

Mild hypochromic anemia is often present, but with specific treatment for polymyalgia rheumatica or spontaneous improvement the anemia is resolved. The most specific criterion is a decidedly elevated sedimentation rate (Westergren method), often exceeding 100 mm in one hour. All observers agree on this finding. When pain and stiffness abate, or when steroid therapy is begun, the sedimentation rate decreases or returns to normal. Although the leukocyte count is usually normal, there may be mild leukocytosis. The cell differential is generally normal, but slight eosinophilia may occur. One observer noted casts (hyaline, granular) on urinalysis in 4 of 18 patients.¹⁴

Tests for rheumatoid factor have been negative in all instances, except for Bagratuni's⁶ and Bruk's²⁶ reports of several positive Rose-Waaler tests. One patient with granulomatous temporal arteritis had rheumatoid factor in the lesion but not in serum.²⁷ Mild decrease in serum albumin and increases in alpha-1 and gamma globulins occur, while there is pronounced increase in alpha-2 globulin. With therapy, these protein changes revert to normal. Serum fibrinogen increases significantly, often to greater than 900 mg per 100 ml. Antinuclear antibodies, LE preparations, calcium, phosphorus, alkaline phosphatase, and muscle enzyme determinations have all been normal. One report of abnormal liver function studies has ap-

peared.²⁸ Results of electromyography and examination of bone marrow aspirate have always been normal.

Radiography

X-ray changes showing osteoporosis and degenerative arthritis have been noted to be consistent with the patients' age. With the possible exception of Bagratuni,¹⁶ investigators have noted no evidence of active arthritis. Selected angiographic studies have revealed stenosis at the sites where murmurs had been heard over large vessels²⁵ and arterial narrowing of the major arteries in the lower extremities was also noted in a few cases of polymyalgia.²²

Pathology

Muscle biopsy, as was noted earlier, shows no evidence of degenerative or inflammatory changes either in the muscle or in the intramuscular vessels. This is probably due to the small caliber of these arteries, whereas the changes of giant cell arteritis occur in medium and large sized arteries. In two patients, however, perivascular infiltrates of lymphocytes were present in muscle septa.²¹

Arterial biopsy has been performed by various investigators, as previously mentioned. In one case with intermittent claudication, there was a panarteritis with pronounced intimal proliferation producing symmetrical narrowing of long portions of the major arteries to both lower extremities.²² Giant cells were found in the subclavian artery,²⁵ suggesting disseminated arteritis. At post-mortem examination of three patients who died of other causes after having been followed for up to five years for polymyalgia rheumatica, a disseminated giant cell arteritis of the aorta and some of the great vessels from the aorta were noted.²⁹ One case of granulomatous myocarditis was found at autopsy.³⁰

Most rewarding have been the results of a temporal artery biopsy, already discussed. Microscopically, findings consisted of panarteritis with giant cell granuloma and fragmented elastic fibers in the media as well as intimal thickening producing a narrowed lumen with thrombus formation or intimal swelling (Figures 1 and 2). Negative biopsy may be due to patchy or segmental involvement of arteries, so that specimens might be taken from "skip" areas. Biopsy from other than temporal arteries has shown only non-specific changes.

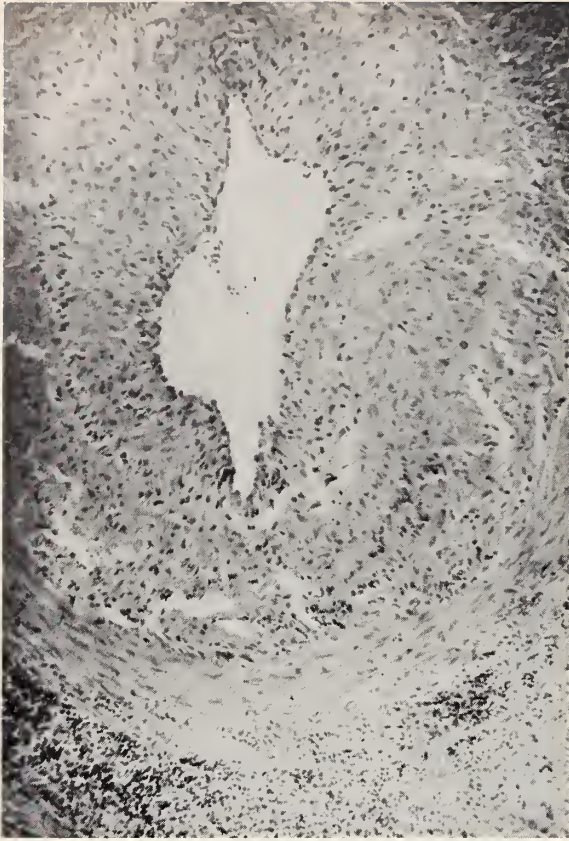


Figure 1.—Temporal artery showing acute arteritis, intimal and medial edema and some inflammatory reaction. Pronounced inflammation in the adventitia.



Figure 2.—Sagittal section. Partially organized and adherent thrombus in an inflamed temporal artery.

To date only one study of temporal arteries has been performed in a random group of autopsy examinations.³¹ Progressive degenerative changes, reportedly indistinguishable from those of healed arteritis, were noted in temporal arteries of aged patients. All layers of the vessel wall were involved but giant cell changes were not present, except in two patients, in whom giant cell aortitis was likewise found.

One mechanism postulated for muscle pain and tenderness is that inflammation in arteries supplying the muscles may cause ischemia and pain without any histological changes. According to this postulation, involvement of subclavian arteries results in shoulder girdle pain and iliac artery involvement in pelvic girdle pain.

Electron microscopy was performed on the liver biopsy specimen in the one reported case in which results of liver function studies were abnormal.²⁸ Whereas light microscopy was normal, electron microscopy revealed changes in the ultrastructure of liver cells, mainly in the mitochondria and en-

gastoplasm. Also noted were abnormal glycogen distribution and abundant lipofuscin.

Differential Diagnosis

The early diagnosis of polymyalgia rheumatica may be difficult when only one group of muscles are affected. Gordon²¹ discussed this matter in his excellent review article. Cervical spondylosis is common in the older age group which also suffers from polymyalgia, and the differential diagnosis of these two conditions may be very difficult indeed. Cervical osteoarthritis is suggested by x-ray studies showing narrowing of joint spaces and osteophytes, whereas a high ESR and, of course, tenderness of cranial arteries or a positive artery biopsy indicates polymyalgia. The presenting manifestations of multiple myeloma are back pain and accelerated ESR, but proteinuria, abnormal bone marrow showing increased plasma cells, a gamma spike on protein electrophoresis and x-ray changes of the spine are also expected. Nerve root pressure due to metastatic carcinoma of the vertebra or a

lumbar disc prolapse will present with pain and, sometimes, increased sedimentation rate, but in such cases abnormalities are found on routine x-ray examination and myelography. Degenerative peri-arthritis of the shoulder is unilateral, constitutional symptoms are absent and the ESR is usually normal.

Systemic lupus erythematosus (SLE) and periarteritis nodosa may be considered in the differential diagnosis because of myalgias, arthralgias, constitutional symptoms and accelerated ESR. In SLE, the patients are younger, LE preparations or ANA are usually positive and many other symptoms are manifested. In periarteritis, one may find evidence of renal or pulmonary disease and necrotizing vasculitis. These patients are often quite ill and do poorly whatever the therapy. Polymyositis presents with muscle weakness and less frequently with pain and stiffness. In addition, there are often muscle atrophy, elevations of serum muscle enzymes (for example, SGOT, CPK, aldolase), electrocardiogram changes and abnormal muscle biopsy specimens. In carcinomatosis, systemic symptoms and accelerated ESR are present, but the response to therapy is poor.

Chronic brucellosis is characterized by arthralgias, malaise, low grade fever, sweating and muscle pains. However, the sweating is more pronounced and the pains are milder than in polymyalgia rheumatica, without especially affecting shoulders or hips. The diagnosis may be established by serologic testing or cultures. Rheumatoid arthritis in elderly people is similar to polymyalgia rheumatica. Frequently the ESR is accelerated, some of the patients have anemia, and shoulder involvement is present in more than half of them. However, other manifestations of joint disease, radiographic changes and abnormal serologic tests are also found. The presence of a positive latex fixation in an elderly person is quite common and, hence, may be misleading. Finally, psychoneurosis may be simulated because of vague pains and absence of objective findings. In this latter condition the ESR is normal.

Course

Even without treatment, polymyalgia rheumatica is usually self-limited, lasting from two to four years, with complete recovery.²¹ Bagratuni,¹⁶ however, found the mean duration of symptoms in his 50 patients to be seven years. It is possible that with the relationship between polymyalgia rheu-

matica and temporal arteritis becoming more apparent, severe sequelae such as blindness may be reported in association with the disease in the absence of appropriate steroid therapy.¹⁵ Vascular thrombosis may also occur in other vital places.³²

Complications

Perhaps temporal arteritis should not be listed as a "complication" of polymyalgia rheumatica, since each represents a segment of the same entity or similar manifestations of disseminated giant cell arteritis. Temporal arteritis occurs in at least one-third of patients with polymyalgia rheumatica.¹³ Blindness is said to be a very common finding in temporal arteritis—it occurred in 73 of 175 patients reported by Hollenhorst³³ due to arteritis of the ophthalmic arteries. Forty to fifty percent of patients with temporal arteritis have visual involvement³⁴ and the loss of vision may be sudden and irreversible. Eye involvement has occurred in cranial or temporal arteritis even in cases in which temporal biopsy was negative.³⁵

Classical temporal or cranial arteritis is manifested by severe head pains; by tenderness over the course of temporal and occipital arteries, which may be reddened, thickened and non-pulsatile; by failing vision; by myalgias, which usually precede the arteritis by weeks to years; and by undue carotid pressure sensitivity, scalp tenderness, fever and necrosis;³⁶ symmetrical peripheral neuropathy manifested by diminished sensation and weakness of several or all extremities and decreased deep tendon reflexes;³⁷ and ophthalmoplegia.³⁸ Examination of fundi may be negative or may reveal papillitis, exudates, perivasculitis with "sheathing" of vessels and optic atrophy. Laboratory findings include accelerated ESR, increased globulins and hypochromic anemia.

However, cranial arteritis may present in other than the classical way. Headache may be absent if the occipital arteries are not yet involved. Lingual arteritis produces recurrent ischemic episodes manifested by paroxysmal blanching of the tongue.³⁹ Other arteries may be involved with giant cell changes, including the aorta, internal and external carotids, iliacs, coronaries, occipitals and retinal vessels. These changes may produce, among others: aortic incompetence due to aortic arteritis; coronary artery disease; deafness and ear pain; and strokes. Elderly people are more subject to vasculitis involving the aorta and its main branches, especially the cranial vessels.⁴⁰

Treatment

Corticosteroids produce prompt and dramatic relief of myalgic symptoms within days in virtually all cases. In addition, constitutional symptoms abate, ESR decreases and vascular complications (visual, cerebral, coronary, and others) are prevented. Gordon²¹ followed eight patients without steroids and they remained symptomatic for periods of two to four years. He treated 13 patients with steroids and all responded. His regimen consisted of 30 to 40 mg of prednisone for 10 to 20 days, then tapering, and stopping the drug within five weeks. In some, a complete, sustained remission was accomplished with one course. When symptoms recurred, myalgias were less severe. Several patients required repeated steroid courses and in one patient five courses were needed. Long courses were not used because of the danger of osteoporosis in the elderly.

Fessel and Pearson¹⁵ advocated performing temporal artery biopsy and then treating all those persons who had positive biopsy with 40 to 60 mg of prednisone daily for 12 weeks. They expressed belief that most visual complications occur within 12 weeks of the onset of general symptoms of giant cell arteritis. A maintenance dose of 7.5 to 10 mg daily may be required for relief of pain over an extended period.

Wilske and Healey¹⁴ use 30 mg of prednisone daily for one month in polymyalgia rheumatica. They then decrease by 5 mg every two weeks to a dose of 10 mg, and then by one mg every week, for a total course of approximately six months. They use salicylates and phenylbutazone as adjuncts while tapering steroids. Only 4 of 18 patients were able to discontinue steroids within six months, many requiring maintenance doses of more than 10 mg of prednisone for months.

When temporal arteritis was definitely present, steroids resulted in abatement of headache and myalgias and return of temporal artery pulsations.⁴¹ Prompt use of steroids usually prevents sudden blindness, the incidence of blindness decreasing by 50 to 75 percent.⁹ A patient with intermittent claudication was started on 40 mg of prednisone daily and after 13 months was still taking 10 to 15 mg daily. Claudication abated and there was arteriographic evidence of improvement of arterial narrowing. Once during the period when steroid dosage was reduced to below 10 mg daily, symptoms of claudication recurred.²²

The use of salicylates has given unpredictable

results in most patients. However Bagratuni found them to be efficacious.¹⁶ Physical therapy may be helpful. Phenylbutazone and oxyphenbutazone are satisfactory in alleviating myalgia, although not as good as steroids. However, these two drugs are dangerous because they masked the development of temporal arteritis in four patients, in whom some visual loss resulted.⁴²

Prognosis

The usual prognosis is favorable, with complete recovery the rule when steroids are instituted early. Total cessation of myalgias and other constitutional symptoms and relief of arteritic manifestations occur.

Illustrative Cases

Case 1. A 55-year-old woman had a history of progressive fatigue for one year and severe myalgias for six months. Myalgias began in the legs, knees and anterior thighs and more recently in the biceps, triceps, deltoids, groin, popliteal areas, medial thighs and in the posterior neck. She denied headaches, joint swelling or pain, but had noted morning gel and stiffness lasting approximately an hour. Diffuse tenderness and hypersensitivity of the scalp were present for six months and a tender area in one temporal artery had developed several weeks before examination. Medications she was taking included indomethacin, 25 mg four times a day, and aspirin, 30 to 40 grains daily.

Past history was unrevealing, except for an episode of left ophthalmoplegia ten years earlier, which improved over several months.

On examination, the left temporal artery was not prominent or readily palpable except just above the outer one-third of the left eyebrow where it was found as a tortuous, enlarged, slightly red, tender vessel. The optic discs and fundi appeared normal. All peripheral joints were normal. Muscular tenderness was elicited on compression of shoulder or pelvic girdle areas.

The ESR was 47 mm in one hour and both the latex fixation and ANA were borderline but not definitely positive. A left temporal artery biopsy showed intimal edema, pronounced narrowing of the lumen, elastic fragmentation in the media, adventitial inflammatory cell infiltrates and the presence of giant cell-like granulomata (Figures 1 and 2). Prednisone was instituted, 60 mg daily, with excellent response; the patient was essentially

asymptomatic within 48 hours. Over the next several weeks the dosage was tapered to 15 mg daily, at which time minimal symptoms recurred and the ESR was 28 mm in one hour. On 20 mg of prednisone daily she remained essentially asymptomatic and the cranial arteries were no longer tender.

Case 2. A 75-year-old man was admitted with blindness of the left eye of four days duration. Three weeks earlier, aching pains had developed in the shoulders, neck, back and upper arms. These were associated with throbbing headaches that started at the vertex and radiated to the left eye and the left occiput. The patient also noticed an uncomfortable sensation on the left side of the head when brushing the hair or touching the scalp in that area. The various pains were rather mild and were readily relieved by 40 to 60 grains of acetylsalicylic acid per day. Two weeks after the onset of symptoms the patient was seen by a physician, who obtained laboratory studies with normal results except for an erythrocyte sedimentation rate of 35 mm in one hour (Wintrobe method). A week later the patient suddenly noted complete blindness of the left eye and was referred to the hospital. The headaches subsided spontaneously at about this time, but the other pains persisted.

There had never been previous symptoms of arthritis or related disorders. The family history was noncontributory.

Physical examination showed blurred disc margins bilaterally. A cerebral neoplasm was excluded by x-ray studies of the skull, electroencephalography, brain isotope scan and spinal-fluid examination.

During the first week in the hospital the patient had only slight, generalized aching discomfort. On the twelfth day vision in the right eye decreased. Visual loss was rapidly progressive during the next 48 hours. A biopsy of the left temporal artery was made, prednisone (60 mg daily) was started, and stellate-ganglion block was performed. After the institution of corticosteroid therapy the musculoskeletal symptoms subsided completely and the blindness did not progress, although vision did not improve. The temporal arteries, which had not been noticeably tender, did not appear to change in character. During the next nine months the patient continued to receive 40 mg of prednisone daily. The vision of the right eye did not further decline, but total blindness per-

sisted in the left eye. The musculoskeletal symptoms in the neck, shoulders, arms and upper back have not returned.

Pertinent laboratory findings during the hospital course included normal hemoglobin and hematocrit and a creatinine of 1 mg per 100 ml. LE cells and antinuclear antibodies were absent, and the latex fixation test was negative. The sedimentation rate was 36 mm in one hour. The temporal artery biopsy showed acute and chronic inflammatory cells in all layers of a thickened blood vessel wall, with fibroblastic proliferation of the media, edema of the endothelial lining and thrombus formation. The features were consistent with temporal arteritis.

The first patient had myalgias and temporal artery tenderness without any ophthalmic manifestations, whereas in the second patient unilateral blindness developed shortly after the onset of myalgias. Possibly the vision in the other eye was preserved by prompt treatment with prednisone.

Conclusion

The current status of polymyalgia rheumatica remains somewhat unclear in the literature, because of differences in nomenclature and differing views regarding its relationship to cranial arteritis. It seems that the evidence linking these two conditions is overwhelming and that treatment for polymyalgia rheumatica should be aimed at preventing the sequelae of arteritis, whether or not biopsy evidence of arteritis is found. Since involvement of arteries may be patchy, a negative biopsy does not rule out the presence of arteritis. Polymyalgia rheumatica may be a form of arteritis in which cranial and other large arteries, and even the aorta, may be involved at various stages of the disease.³²

The dosage and duration of steroid therapy will have to await further and longer follow-up studies. Meanwhile, it seems most appropriate to treat with moderately high doses of steroids, probably 30 to 60 mg of prednisone daily, for at least three months and then taper to 10 to 15 mg daily for a total of six months to a year, with discontinuance sooner if myalgias disappear. This proposal is made even though it is recognized that the present criteria for the diagnosis of polymyalgia rheumatica are incomplete. More studies on the incidence of arteritic changes in polymyalgia rheumatica are needed. Also, other causes for acceleration of ESR should be vigorously sought before steroid therapy

is given to an elderly person. Finally, it would again be worthwhile examining temporal arteries in a large random group of elderly patients, at autopsy, to fully evaluate the changes that reportedly occur with aging.

Polymyalgia rheumatica may be more common than it has been thought to be. It should be thought of when an elderly person presents with pain in the neck and shoulders, especially in conjunction with an unusually accelerated ESR.⁴³

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RECTOVAGINAL FISTULA FROM CANCER

"Once a patient [with pelvic cancer] has developed a rectovaginal fistula either from radiation alone or as a result of combination therapy, there will be very few fistulas, I think, that you can close successfully. In a majority of instances, you'll be wise to settle for a permanent colostomy. [One of my colleagues has] an elaborate procedure in which he developed a whole tag of omentum and tried to interpose that between the rectal defect and the vaginal wall; but I think there are few of us who are qualified to take on this procedure. I've done exenterations at times for extensive radiation damage, including those with the rectovaginal fistula; but for the most part I believe that the colostomy is indicated."

—LANGDON PARSONS, M.D., Boston

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Diseases from Vietnam

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* The Medical Grand Rounds this morning is being devoted to the medical fallout of our brisk foreign policy. The presentation of patients as well as the discussion will be given by Lieutenant Colonel John J. Deller. Dr. Deller we know as an old friend, since in addition to his army training he spent one year as a Fellow in Endocrinology and Metabolic Diseases here at the University of California. We are delighted to welcome him back and have him introduce both his topic and his patients.

DR. DELLER:† Thank you, Dr. Smith.

This morning I would like to review some of the medical problems seen in this country but which have originated in Southeast Asia. These problems have significance for physicians here in San Francisco; they are not remote tropical diseases found only in a textbook. Currently there are over 500,000 Americans in Vietnam. With the present rotation policy, these 500,000 Americans will return to the United States within a year, and with them will come tropical diseases.

Basically the medical community is faced with two problems: the recognition of diseases imported into this country for the sake of the "host patient" himself and, less immediate but more far-reaching, a significant public health problem in the introduction of new diseases into this country. I will deal mainly with the first of these considerations and only touch upon the potential of the latter.

It takes less than 20 hours to fly from Saigon to San Francisco. This brings the fighting-front fairly close. Thus, it is not at all unreasonable for us to expect any disease seen at a battalion clearing company or an evacuation hospital in Southeast Asia

to appear at a community hospital in this country. Realization of this fact emphasizes the importance of tropical medicine in the United States, not only now but in the future. With increasing air traffic around the world, tropical diseases will be seen more and more in this country. Only by having a keen awareness of these diseases will we be able to make prompt, accurate diagnoses. Because some of these diseases are potentially fatal, early recognition may be critical.

In the limited time available, I shall concentrate on a small group of febrile illnesses which, because of their long incubation period, are likely to be seen in this country. Many of these patients will be seen by private physicians because most of the returning soldiers are either discharged from the service within a few days of arrival in the States or are given a 30-day leave.

It was from necessity that we became interested in tropical febrile diseases at the 93rd Evacuation Hospital in Vietnam. At first we had only the usual textbook knowledge of these diseases. It was very frustrating to admit large numbers of patients having a variety of indistinguishable febrile illnesses. We studied a number of these cases to establish some diagnostic criteria. When you read the chapters on tropical medicine in the standard textbooks of medicine, you find that all of the tropical febrile diseases seem to melt together and that there appear to be very few distinguishing features. In order to organize an approach to these illnesses, I have grouped them into five major disease categories (Table 1). The major arbovirus diseases seen in Southeast Asia are two in number: dengue, with which you are probably familiar, and chikungunya, which is esoteric by American standards. These in addition to scrub typhus, leptospirosis, and malaria constitute the biggest medical problems. Melioidosis is of significance because of its

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seriousness. (This list omits venereal disease, by far the commonest infectious disease among troops in Southeast Asia.)

Table 2 is taken from our original study in which we attempted to define the various clinical manifestations of these febrile tropical illnesses. The diagnoses were proven by virological, bacteriological, or serologic tests.¹

Dengue

Dengue is the most common arthropod-borne virus disease affecting our troops in Southeast Asia. A widely known disease, dengue was first recognized in the 1780s in Philadelphia—certainly no tropical climate. Since that epidemic the disease has cropped up from time to time throughout the country, mostly in army camps. The mosquitoes necessary for transmission of this disease do exist in the United States.

In Vietnam we were confronted with the problem of differentiating dengue from a number of more serious diseases. As will become apparent, fever, chills, and headache are characteristic of most of the tropical febrile diseases. However, it is important to know how high the fever goes and where the man was when he became ill, because, knowing these two simple facts, one can often dis-

tinguish between arborvirus diseases on the one hand and the “jungle-borne” diseases on the other. For example, patients with arborvirus infections rarely have temperatures above 104° F. This is an extremely important differential point because almost invariably a patient with malaria will have a fever rise above 104° F within the first 48 hours.

The arborvirus diseases, dengue and chikungunya, are transmitted primarily by the Aedes mosquito, an urban dweller. As a consequence, these diseases are not likely to be encountered in the jungle but are most frequently seen in an urban area or base encampment. Thus by asking the patient where he was within the 2 or 3 weeks preceding onset of symptoms, one can often predict whether the patient has an arborvirus disease or a “jungle-borne” disease such as malaria, leptospirosis or scrub typhus.

The symptoms of dengue are not distinctive. Three-quarters of the patients have a “flu-like” illness with malaise, backache, anorexia, fever, and often severe frontal headache. They may present with lymph adenopathy, an important physical finding because patients with malaria do not have adenopathy and in patients with scrub typhus adenopathy develops only after several days of illness. A fleeting macular rash is present in at least one-third of the patients, and spontaneous petechiae occurring within this setting, especially on the lower extremities, are almost diagnostic for the arborvirus diseases. The tourniquet test may be positive in patients with dengue without an associated reduction in platelet count.

The course of dengue is variable. Generally fever and symptoms subside within 5 to 7 days, and few patients have a prolonged convalescence.

TABLE 1.—Major Febrile Tropical Illnesses in Southeast Asia

Arborvirus Diseases
Dengue
Chikungunya
Scrub Typhus
Leptospirosis
Malaria
Melioidosis

TABLE 2.—Differential Features of Patients Having Dengue, Chikungunya, Scrub Typhus, Leptospirosis, and Malaria

	Dengue	Chikungunya	Scrub Typhus	Leptospirosis	Malaria
Epidemiology					
Camp, urban	†††	†††	—	—	—
Jungle	—	—	†††	†††	†††
Fever, F					
<104	†††	†††	†	†††	—
>104	—	—	††	—	†††
Arthralgias	—	†††	—	—	—
Tender adenopathy	†† (Early)	†††	††† (Later)	†	—
Tender liver or spleen	—	—	††	††	†††
Rash	†	††	††	—	—
Petechiae or positive tourniquet test	†	—	—	—	—
Leukocyte count per cu mm					
<5,000	††	††	—	—	—
>5,000	†	†	†††	†††	†††
SGOT >50 units	—	—	—	—	††

SGOT = serum glutamic-oxaloacetic transaminase; — = less than 25 percent; † = 25 to 49 percent; †† = 50 to 74 percent; ††† = 75 to 100 percent.

Adapted from Annals Inter. Med., 66:1129, 1967 and USARV Med. Bull., 2:23, 1967.

Chikungunya

The second arbovirus disease which may be acquired in Vietnam and transported back to this country is chikungunya. This disease was first recognized in Tanganyika in 1952 when an epidemic characterized by high fever and severe polyarthritis occurred among the natives. It was, however, self-limited. Fortunately, Dr. Ross² collected blood from many of the affected patients along with pools of *Aedes* mosquitoes, and in 1956 he isolated a new virus to which the name chikungunya was given—the natives' description, which means "that which bends up the joints."

Since the recognition of that original epidemic, chikungunya has been identified throughout South-east Asia, southern parts of Africa, and India. It has had a wide spectrum of clinical features ranging from severe polyarthritis, which so far as I know has been self-limiting, to a dengue-like illness with mild arthritis, to hemorrhagic fever. The same virus has been cultured from all of these clinical varieties.

The one feature that distinguishes this disease from dengue is the arthritis. Even though dengue has been referred to as "break-bone fever," it is not associated with true arthritis. Severe myalgias and perhaps arthralgias may occur with dengue, but not arthritis. The polyarthritis of chikungunya is of great interest, for it represents an example of a known viral disease, from which an organism can be readily cultured, that can mimic both rheumatoid arthritis and acute rheumatic fever. It is very much like the epidemic polyarthralgia, which again mimics rheumatoid arthritis, reported in Australia and New Guinea. Chikungunya so closely resembles rheumatoid arthritis that our first three patients presenting with fusiform swelling of the proximal interphalangeal joints and bilateral synovitis of the wrists were initially diagnosed as having acute arthritis.³ However, patients with chikungunya improve spontaneously and, although the arthritis may linger for several weeks, it does not develop into chronic arthritis. However, it is conceivable that if a viral disease similar to chikungunya had a strong antigenic potential, it could initiate an auto-immune reaction and lead to a chronic form of arthritis.

Except for the arthritis, chikungunya in American troops has been a mild dengue-like illness. It has not produced the severe crippling arthritis of the type reported in Tanganyika, nor has it caused hemorrhagic fever as occurs in dengue. It is a dis-

ease that should be considered in a Vietnam veteran who has an acute febrile illness.

It is important to recognize these two arbovirus diseases in order to distinguish them from diseases that are more important from the standpoint of morbidity and mortality.

Scrub Typhus

Scrub typhus is caused by a mite-borne rickettsia and presents with a typical triad of rash, eschar, and a positive therapeutic response to tetracycline. With these prominent features, it is usually easy to diagnose; unfortunately, not all cases behave this simply. Sometimes the eschars are hidden and may be overlooked on physical examination.

Like malaria, scrub typhus occurs in the jungle. The mites that carry the rickettsial organism breed in heavily forested areas of Vietnam; hence a history of a jungle environment is important. It has been said that these mites live and breed on the larvae of the *Anopheles* mosquito. I am not sure that this theory holds up, but at least the two diseases commonly occur together; indeed, malaria and scrub typhus may occur simultaneously in the same patient. The fever, chills, headache, malaise, adenopathy and backache common to all of these tropical diseases are also characteristic of scrub typhus. In addition, severe conjunctival injection, which we usually associate with leptospirosis, is common in scrub typhus. The most important features are a macular rash, which is usually not as fleeting as the rashes of the arbovirus diseases, and an eschar. The eschar typically resembles a cigarette burn. It is not surrounded by significant inflammatory reaction and usually has a black necrotic center with a narrow rim of erythema. There is no associated lymph angitis or lymph adenitis. This lesion is important to recognize because in melioidosis, which I will discuss later, a skin inoculum can present in a similar manner, except that there is a much greater reaction and associated lymph angitis.

It is important to treat suspected scrub typhus with tetracycline. Of the tropical diseases, only scrub typhus responds dramatically to tetracycline therapy (1 gram every hour for four doses followed by 1 gram every 6 hours for 7 days). Within 48 hours, and often within 12 hours, there is a dramatic drop in fever. It is important to treat scrub typhus early, for if the disease goes untreated for 2 weeks, there is an alarming morbidity. Most of our patients in whom the disease was not recog-

nized for 2 weeks had to be evacuated to the United States and were ill for 6 to 8 weeks.

Leptospirosis

In leptospirosis the patient is not bitten, but has only to come in contact with leptospires breeding in the mud banks and rice paddies. Leptospirosis closely mimics dengue and scrub typhus and has very few distinguishing characteristics. It has been called "pseudodengue." It most closely mimics scrub typhus because of the generally high, spiking fevers. Conjunctival suffusion is an important sign, but it does not distinguish leptospirosis from scrub typhus. Gastrointestinal complaints and hepatic tenderness are common, which makes for confusion of this disease with malaria. A laboratory finding of leukocytosis is occasionally helpful, since most of the other tropical diseases are characterized by a normal leukocyte count or by leukopenia.

Leptospirosis actually encompasses an entire spectrum of diseases from a benign, self-limited form such as our troops are experiencing to a severe, hemorrhagic disease with severe jaundice and renal failure. Since our troops fortunately have acquired the benign form, there have been no serious complications. The benign form of leptospirosis is self-limited and requires no specific therapy.

Malaria

Malaria is the tropical disease which is of most concern to military physicians because it accounts for the largest number of patients. The malaria seen in Vietnam may be quite different from that seen in San Francisco. About 98 percent of the cases of malaria diagnosed in Vietnam result from *Plasmodium falciparum*, whereas 80 percent of the cases seen in this country result from *Plasmodium vivax*. The reason for this difference is the chloroquine-primaquine chemoprophylaxis or "suppressive therapy" program that is being used in Vietnam. Usually once a soldier leaves the endemic area, he neglects to take the drugs, even though he is given an 8-week supply, and with discontinuance of therapy the disease becomes manifest. Of 29 consecutive patients with vivax malaria admitted to Letterman General Hospital within the past year, not one had taken the medication after getting off the airplane! Subsequently a larger group of patients who did not have malaria after returning to this country were surveyed, and 60 percent of them had not taken the chemoprophylaxis after leaving Vietnam.⁴

The reason so much falciparum malaria is seen in Vietnam is that the current drug therapy is not suppressive for *Plasmodium falciparum*. In the last year there have been more than 2,000 cases of malaria diagnosed in American soldiers in this country. This figure could probably be expanded many times by including in it those patients who have left the service and therefore are not reported to the Surgeon General.

Malaria is generally easy to diagnose. All one needs is a high index of suspicion, a blood smear, and a technician or physician who knows how to interpret the smear. The majority of patients with malaria will have fever above 104° F within the first 72 hours of illness; frequently the temperature goes to 105° or 106° F. The differentiating feature is that such elevations are extremely rare with the other tropical diseases. Of course the shaking chill, a hallmark of malaria, is generally present, accompanied by headache and a variety of gastrointestinal complaints in over three-quarters of the patients. The most remarkable feature about the physical examination is the absence of specific findings. Except for percussion tenderness over the liver or spleen, or both, the examination is usually negative unless the patient has one of the major complications. Notably absent are the "typical" fever patterns and splenomegaly found in textbook descriptions of malaria. This absence is attributable mainly to prompt diagnosis and early treatment.

For the diagnosis of malaria, a high index of suspicion is critical. Once malaria is considered, a series of blood smears, both thick and thin, should be done to confirm the diagnosis. If you're lucky, on a thin smear you will see typical ring forms. Frequently, however, the thin smear will not reveal ring forms within the erythrocyte, and a thick smear will be necessary. The parasites may be fragmented and difficult to diagnose. In falciparum malaria the ring forms are only about one-fifth as large as the vivax forms. The gametocytes of falciparum malaria, however, are quite typical and easily recognized. Unlike the diseases previously discussed, which manifest themselves within 3 weeks, malaria may have a long latent period. Most of the vivax malaria in this country is diagnosed in patients who have left an endemic area more than 50 days before; therefore, this disease is very likely to be seen by private physicians.

The treatment of malaria has undergone several changes since the appearance of resistance strains

of *Plasmodium falciparum* in Vietnam. Currently, however, the proper treatment can effect a cure in probably 98 percent of cases. In my personal experience with more than 1,200 patients at one hospital, 20 of whom had cerebral complications and three of whom had renal failure, there were no fatalities. Standard treatment for vivax malaria has not changed, as *Plasmodium vivax* has not demonstrated any resistance to chloroquine and primaquine. *Plasmodium vivax* continues to go through reproductive cycles within the reticulo-endothelial system; therefore, primaquine is given for at least 14 days in an attempt to eradicate the parasites in this "exoerythrocytic phase."

The treatment schedule for *Plasmodium vivax* infection is as follows: chloroquine phosphate, 1.0 gram (600 mg base) immediately, followed by 0.5 gram in 6 hours and 0.5 gram daily for 2 days. Primaquine, 15 mg base, is given daily for 14 days.

Since as high as 50 percent of *Plasmodium falciparum* infections acquired in Vietnam have been relatively resistant to chloroquine, patients with this infection must be treated with quinine. Quinine, when used properly, is a relatively safe drug. When it is used alone, there is perhaps a 5 to 10 percent failure rate; however, the addition of pyrimethamine (Daraprim®) and possibly a sulfone (Dapsone®) or sulfa drug will approach a 100 percent cure rate for initially treated *Plasmodium falciparum*. Currently, triple therapy for falciparum malaria is recommended. The treatment schedule is as follows: quinine, 650 mg every 8 hours for 10 to 14 days, followed by pyrimethamine, 25 mg, every 12 hours for 2 to 3 days and Dapsone®, 25 mg, given daily for 28 days. Many patients who were treated for *Plasmodium falciparum* in the past have had "recurrences" with *Plasmodium vivax* simply because they did not receive any primaquine.

Table 2 reviews the major points in differential diagnosis of the disease most likely to mimic malaria in a person returning from Vietnam. Where the infection was acquired and how high the temperature rose may be the two most important clues as to whether one is dealing with a treatable infection (malaria or scrub typhus) or a self-limited one.

Melioidosis

Melioidosis may be relatively new to most of you. It was originally recognized in Rangoon in

1912 by Whitmore and Krishnashwami, who reported on a number of street beggars dying with what appeared to be distemper because of the tremendous frothy sputum produced before death. A glanders-like microorganism was subsequently isolated and given the name *Malleomyces pseudomallei*. This disease was next recognized about 5 years later in ante mortem studies by Fletcher and Staunton in Malaya in 1917. Melioidosis has subsequently been found in a variety of forms, most simply classified as follows:

- Acute—pneumonic and septicemic
- Chronic—pulmonary and systemic
- Subclinical—serologic evidence only

The acute form can present as overwhelming pneumonia or as septicemic illness which usually terminates as pneumonia. The chronic variety can masquerade as tuberculosis. This is the type with which I think we should concern ourselves because this is the type that may well be seen here in San Francisco. The chronic variety may also present with manifestations such as chronic draining abscesses or osteomyelitis. It has also been shown that there is an "iceberg effect" in this disease, in that there have been a large number of cases with only serologic evidence of past exposure to this infection. In one Thailand study, approximately 8 percent of the population tested had serologic evidence of previous contact with this organism. Although we are not seeing a large number of cases of melioidosis, there have been more than 60 cases reported since May 1966, in Americans in Vietnam or recently returned from there. It is an important disease because it may be lethal in the acute form and also because of the possibility of transplantation into this country. The organism is ubiquitous.

A keen awareness of the clinical spectrum of melioidosis is the key to diagnosis. A chest roentgenogram will often provide the immediate clue. The organism *Pseudomonas pseudomallei* will grow readily on blood agar media; in fact, sometimes it grows so readily that it is thought to be a contaminant. A smear from the culture, stained with either Gram's or Wayson's stain, provides a clear-cut diagnosis in most cases. The organism appears as small pleomorphic, Gram-negative, bipolar rods that resemble small safety pins. Further identification can be made by sugar fermentation studies or specific serologic tests.

I would like to review briefly the major ways in which this disease may present. In our febrile dis-

ease study, we encountered two cases of the septicemic illness which presented with a cutaneous ulcer (presumably the site of entry of the organism), spiking fever, tremendous cellulitis and lymph angitis, and eventually meningitis and pneumonia. The two patients died without diagnosis having been made. Although they were treated with a large number of antibiotics, there was no obvious effect on the illness. This disease in its septicemic form is almost uniformly fatal when unrecognized.

The clinical course of the acute pneumonic variety varies from death within hours to death within days. It is an overwhelming infection; in fact, it is the most rapidly progressive pneumonia that one is likely to encounter. We saw one patient who had acquired this disease, so far as we know, within 5 hours of his death. In this rapidly progressive form, the disease is probably untreatable and is very much like plague pneumonia.

The form of disease which we are now seeing in this country is the chronic, more benign pulmonary infection which often presents with cough, low-grade fever and a roentgenographic appearance which immediately conveys the impression of tuberculosis. A negative tuberculin test and a history of travel to an endemic area should alert one to this disease.

The treatment of *Pseudomonas pseudomallei* infection will vary with the clinical type of disease. When we were first confronted with the acute varieties in Vietnam, we used standard antibiotic schedules, including novobiocin and chloramphenicol. Despite such therapy our first five patients died. We found on serum inhibition studies that even in the undiluted serum there was no inhibition of growth of the *Pseudomonas pseudomallei* with the antibiotic schedules used. We eventually found that a combination of massive doses of chloramphenicol, novobiocin and kanamycin was necessary to arrest the overwhelming infection. Doses as high as 12 grams of chloramphenicol, 3 grams of kanamycin and 6 grams of novobiocin are necessary. With such treatment the next five patients survived. Such heroic therapy, however, has not been necessary with the more chronic variety of disease. It can be treated with as little as 1.0 gram of tetracycline daily. Naturally, sensitivity studies are required in every case.⁵

In summary, it should be emphasized that one must maintain a high index of suspicion of melioidosis in a patient who has been in an endemic

area. This disease may lie dormant for years. In the French experience in the 1940s the disease was cropping up in France as late as 3 years after the return of troops from Southeast Asia.

QUESTION: What is the policy concerning blood transfusions from Vietnam returnees?

DR. DELLER: I believe the current policy is that no one who has been in an area endemic for malaria should be a blood donor for a minimum of 2 years, and this may be revised to exclude such potential donors indefinitely.

DR. SCHMID:* In cases of leptospirosis, do you have any meningeal manifestations?

DR. DELLER: Yes, meningeal manifestations are seen; in fact, the patients frequently will have what is thought to be meningismus. The same manifestations will be seen in scrub typhus. We followed several patients clinically and found that the lymphadenopathy which developed in the cervical areas after several days is probably what was initially mistaken as meningismus. In a few cases we performed spinal taps, and the taps were negative. I think the tender cervical adenopathy often will be masquerading as meningismus.

QUESTION: Have you witnessed any outbreaks of plague?

DR. DELLER: So far as I know we have had only three cases of plague in American servicemen. As you know, plague immunizations have been quite effective. The current plague immunization program, apparently, is keeping the incidence of plague in the American soldier quite low. Certainly plague is very high in the Saigon area and throughout Southeast Asia. We see large numbers of cases in the population there. I am just hopeful that we will be able to continue with our luck in keeping this disease suppressed in the American population.

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Systemic Lupus Erythematosus

MODERATOR: EUGENE V. BARNETT, M.D.

DISCUSSANTS: GARY KANTOR, M.D., YALE B. BICKEL, M.D.,
RUNE FORSÉN, M.D., AND HARVEY C. GONICK, M.D.

■ *Systemic lupus erythematosus is a polysystemic disease with a high incidence of associated glomerulonephritis. Patients with SLE rarely have the destructive arthritis so characteristic of rheumatoid arthritis. An unusual case is presented in which both glomerulonephritis and destructive arthritis occurred simultaneously, justifying the diagnosis of both systemic lupus erythematosus and rheumatoid arthritis.*

Immunohistochemical studies in lupus glomerulonephritis suggest that the pathogenetic mechanisms involve the deposition of immune complexes containing "nuclear" antigens and antinuclear antibodies in the lesions. The detection of mixed cryoglobulins in the sera of patients with SLE suggests that a portion of the circulating immune complexes may precipitate at reduced temperatures and be detected as mixed cryoglobulins. The therapy of lupus glomerulonephritis with combinations of corticosteroids and azathioprine, though still in an investigative state, holds great promise. Similar abnormalities in diseases of minks and mice and in SLE suggest similar pathogenetic mechanisms in the three species involved. Since the diseases in the lower animals have been associated with persistent viral infection, the investigation of the role of persistent infection in SLE seems warranted.

DR. EUGENE V. BARNETT (Department of Medicine)*: Our task is to report a multifaceted approach to the understanding of systemic lupus erythematosus. I think that, perhaps, when we have completed our discussions, we may decide that the term *systemic lupus erythematosus* is not the name of a disease but rather the title for a series of questions. Dr. Gary Kantor will start by discussing the simultaneous occurrence of systemic lupus erythematosus and rheumatoid arthritis.

Differentiation of Systemic Lupus Erythematosus and Rheumatoid Arthritis

DR. GARY KANTOR (Department of Medicine and Wadsworth Veterans Administration Hospital): The case presented is that of a 46-year-old white, married housewife who was initially seen in the medical clinic five years ago for evaluation of polyarthritis. She was in good health until 1958, when swelling and stiffness developed in the metacarpal-phalangeal (MCP) joints of her hands.

Oral corticosteroid preparations were administered from 1958 to 1961 and then replaced with salicylates. She continued to note intermittent

*Some patients reported in this study were in hospital at the Clinical Research Center of UCLA, CRC Grant No. RR00238.

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joint swelling and morning stiffness. From 1961 to 1963 progressive deformity developed in her hands and feet, with additional involvement of the shoulders, hips and knees. On evaluation in the medical outpatient department in 1963, examination revealed subluxation and ulnar deviation at the MCP joints, swelling of the proximal interphalangeal (PIP) joints of both hands, synovial proliferation and effusion in both knees, additional deformities in the metatarsal phalangeal joints, and subcutaneous nodules.

Laboratory data included a normochromic, normocytic anemia, normal urinalysis without proteinuria or sedimentary abnormalities, latex fixation titer of 1:5120, negative lupus erythematosus (LE) cell preparations, and creatinine content of 0.6 mg per 100 ml. Radiographic studies confirmed the presence of articular erosions involving the wrists, MCP and PIP joints, as well as subluxations at the MCP joints.

In March 1964, synovectomy of the MCP joints of the right hand was carried out. Pathological diagnoses included chronic active rheumatoid synovitis and chronic osteitis. Microscopic hematuria was noted for the first time on this occasion.

In February 1965, an erythematous malar rash, aggravated by exposure to sunlight, developed. Biopsy of a specimen of skin was consistent with LE, revealing small vessel vasculitis. Topical steroids were effective, although exacerbations continued after exposure to sunlight.

In August 1965, urinalysis revealed 2+ proteinuria and a quarter field of red blood cells. The LE cell preparation was positive, and antinuclear antibody (ANA) titer was greater than 1:256. Raynaud's phenomenon developed.

In March 1966, the ANA and latex fixation titers were unchanged, and the LE cell preparation was again positive. A 24-hour specimen of urine contained 4.9 grams of protein. The presence of a subcutaneous rheumatoid nodule was confirmed histologically. A percutaneous biopsy revealed glomerulonephritis consistent with systemic lupus erythematosus, and focal glomerular basement membrane deposits of IgG and beta γ -globulin were demonstrated with immunofluorescent microscopy.¹⁵

During a five-month course of prednisone, 45 mg per day, creatinine clearance fell from 140 to 69 ml per minute, and serum complement remained low. In October 1966, azathioprine in a

maintenance dose of 200 mg per day was added to the prednisone.

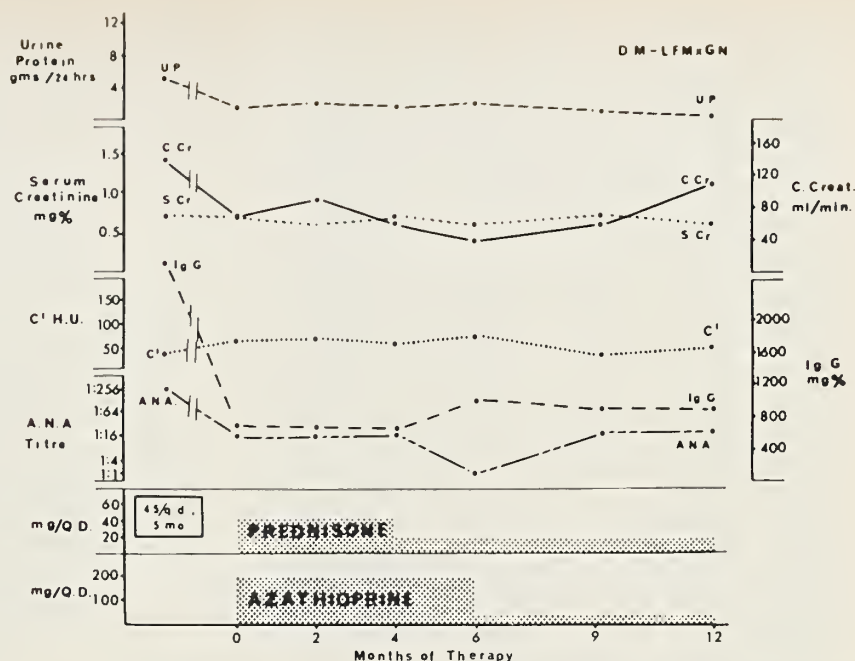
Chart 1 summarizes the patient's course during the first 12 months of azathioprine therapy. The creatinine clearance stabilized, and the serum gamma globulin (IgG) concentration and ANA titer decreased. At present she is taking 100 mg of azathioprine and alternating doses of 10 and 7.5 mg of prednisone per day.

Recent studies showed a creatinine clearance of 85 ml per minute and 24-hour urinary protein of 0.5 grams. A serum complement was 47 C_H50; ANA, positive in undiluted serum only; latex fixation titer, 1:40,980. A repeat renal biopsy 13 months after the institution of azathioprine revealed mild chronic glomerulonephritis with less activity of the glomerular process than noted previously. Focal IgG and beta γ -globulin deposits persisted. The patient has done quite well since the orthopedic procedure. Although she has residual deformities, her functional impairment is relatively mild. There has been no recurrence of the transient hypertension present when she first had some evidence of kidney disease. The rash on her face gives difficulty only upon exposure to sunlight.

This patient's case has several quite unusual features that provide an opportunity to discuss the relationship between rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Before the advent of the LE cell preparation in 1948,³⁵ the diagnosis of SLE was extremely difficult to make. Pathological criteria were important but often unavailable to the clinician. Currently there are several pathological findings which may be helpful.

The presence of hematoxylin bodies has been considered pathognomonic of SLE.³⁷ They appear as small lilac-staining bodies in localized areas of necrosis including the glomerulus, lymph nodes, spleen and endocardium. Phagocytosis of this material by neutrophils is rarely noted *in vivo*. These bodies are not frequently present in the relatively small amount of tissue provided by percutaneous renal biopsy. The wire loop lesion seen within the glomerulus is suggestive of SLE, but nevertheless nonspecific.¹⁶ Periarterial lamellar fibrosis or "onion-skinning" is frequently seen in the spleen,⁴⁸ but may on rare occasions be seen in other processes.⁴¹ Libman-Sacks endocarditis has also been considered specific for SLE.³³ Adequate evaluation of the majority of these tissues

Chart 1. — Summary of patient's course outlining serial determinations of serum creatinine, complement, antinuclear antibody titer, and IgG concentration; creatinine clearance and 24-hour urinary protein. (Courtesy of Dr. James Drinkard.)



remains unavailable to the clinician, and as a result other means must be used in establishing the diagnosis.

Specific criteria for the diagnosis of SLE are not currently in widespread use. In general, however, the presence of multisystem disease, often including glomerulonephritis, in addition to the presence of LE cells or antinuclear antibodies is sufficient to make the diagnosis of SLE. When very sensitive tests are used to detect the presence of ANA,³⁹ a negative test in a patient who is not receiving steroid or immunosuppressive therapy but has active disease excludes the diagnosis of SLE.

A variety of other conditions for which specific or curative therapy is available must be excluded. A young secretary with known discoid LE was admitted to our hospital with fever and acute inflammatory arthritis involving a knee and ankle. The relationship of this episode to her menstrual period suggested a diagnosis of gonococcemia and gonococcal arthritis. She responded to intravenous penicillin, and subsequent blood and cervical cultures confirmed this diagnosis. Although ultimately other evidence suggestive of SLE developed, the utilization of salicylates or even steroids during this episode in lieu of specific antibiotic therapy might have resulted in serious complications.

Subacute bacterial endocarditis with fever, pleuritic pain, central nervous system involvement, arthritis, and focal glomerulonephritis provides

another example. The renal lesion may progress to azotemia or uremia, at which time fever may be minimal or absent, and the diagnosis more difficult to establish. In this situation a negative ANA test excludes the diagnosis of SLE.

In addition, we have seen a young female with well documented multisystem disease clinically consistent with SLE in whom LE cell preparations and ANA titers were negative over a period of several years. Ultimately accelerated hypertension and azotemia developed and she died with uremia. Postmortem examination revealed systemic sclerosis without scleroderma, that is, without cutaneous involvement. During her illness the diagnosis of seronegative SLE had been considered.

The patient whose case was presented at the beginning of this discussion fulfilled the American Rheumatism Association (ARA) criteria⁶⁹ of classic RA, and subsequently evidence diagnostic of SLE developed. In order to evaluate the relationship between these two disorders, charts of patients with either RA or SLE who have been seen at UCLA within the last two years were reviewed. For purposes of comparison, the ARA criteria for the diagnosis of RA were employed, though ignoring the exclusion clause relating to the presence of LE cells. Similarly, a composite of clinical and laboratory criteria was utilized for the diagnosis of SLE. The presence or absence of seven features was noted, including characteristic malar rash, fever, serositis, non-erosive arthritis, small vessel

vasculitis, glomerulitis or glomerulonephritis, and signs or symptoms of central nervous system involvement. The presence of radiographic erosions was not considered an exclusion. The results of LE cell preparations and ANA determinations were noted. The diagnosis of *possible* SLE was utilized in the presence of one clinical criterion and a positive result in one of the above laboratory tests, *probable* SLE with two clinical criteria and one laboratory test, and *classic* SLE with three clinical criteria as well as a positive LE cell preparation. The incidence and titer of rheumatoid factor¹² was also determined in both groups. These data, not including the patient presented, are summarized in Table 1.

Charts of 32 patients with RA were reviewed, including 15 with criteria of classic RA, 14 with definite RA, and three with probable RA. Tests for ANA were positive in 3 of 32 and for rheumatoid factor in 27 of 32 patients studied. Radiographic findings consistent with RA were noted in 22 of 24 patients and included 12 with definite articular erosions. Clinical, laboratory, or pathological evidence of glomerulonephritis was not noted in any patient with RA.

Charts of 47 patients with SLE were similarly reviewed, including 21 with criteria of classical SLE, 23 with probable SLE, and three with possible SLE. Tests for ANA were positive in 44 of 45 patients and for rheumatoid factor in 14 of 47 patients studied. Radiographic studies of the joints were obtained in 14 cases and revealed evidence of subluxation in one patient. However, erosions were not noted in any patient. Nephritis was present in 28 patients.

These data are consistent with a review of the literature since the introduction of the LE cell preparation 20 years ago. Although joint deformity and radiographic changes suggestive of RA have been previously noted in patients in whom the diagnosis of SLE has been considered, documented erosive arthritis is very rare.

Relevant to this observation, the renal service at Wadsworth Hospital saw recently a 74-year-old white man in whom the diagnosis of SLE was made

in 1951 after arthritis, fever and chest pain developed and an LE cell preparation was positive. Joint deformity developed during the next seven years and resulted in MCP ulnar deviation and subluxation. At present, 17 years after the onset of joint symptoms, pronounced deformities persist. Nevertheless, current x-ray films still do not reveal articular erosions, although subluxation at the MCP joint is noted (Figure 1). A positive LE cell preparation at the onset of illness and the current lack of articular erosions would be most unusual in a patient with RA.

In another patient with classic SLE and joint deformity but no radiographic evidence of erosions, synovectomy revealed findings consistent with degenerative arthritis with articular fibrosis. Typical granulation pannus was not present. Other reports indicate that there may be minimal or absent histological changes in the synovium associated with the articular complaints in SLE in contrast to RA.⁴⁸ The absence of pronounced synovial hyperplasia and associated increased intra-articular pressure in SLE may account for the absence of erosions.

Results of numerous studies utilizing percutaneous renal biopsy or postmortem material on consecutive patients indicate that glomerulonephritis does not occur as part of RA.³¹ Renal abnormalities in RA include amyloidosis, interstitial nephritis, papillary necrosis associated with analgesic abuse, and arteriolo or arteriolar nephrosclerosis.⁴⁹

The rarity with which glomerulonephritis occurs in RA has led to the hypothesis that rheumatoid factor in some way alters antigen-antibody complexes, and thereby protects against the development of nephritis.¹⁷ Data from this series does not confirm this concept. Significant titers of rheumatoid factor were noted in 14 SLE patients, six of whom had lupus nephritis, including one patient with a latex fixation titer of 1:40,980.

A prime diagnostic consideration relates to the presence or absence of nephritis in patients with SLE. Without nephritis the manifestations of the disease may frequently be managed with salicylates or low-dose corticosteroid preparations. In the presence of renal disease, high-dose steroid or immunosuppressive therapy is considered.²⁰ Although sometimes difficult to distinguish from SLE clinically, RA in association with either diffuse vasculitis, amyloidosis, progressive renal impairment, or positive LE cells, is nevertheless not SLE.

TABLE 1.—Summary of Data in 32 Rheumatoid Arthritis (RA) and 47 Systemic Lupus Erythematosus (SLE) Patients

Disorder	Rheumatoid Factor	Antinuclear Antibodies	Radiographic Erosions	Glomerulonephritis
RA	in 27 of 32	in 3 of 32	in 12 of 24	in 0 of 32
SLE	in 14 of 47	in 44 of 45	in 0 of 14	in 28 of 47



Figure 1.—*Left:* Chalk outline of the fingers, drawn with ulnar deviation passively reduced and both hands pressed firmly on the table to prevent ulnar deviation. *Right:* Radiograph of same hand, revealing subluxation at the metacarpal-phalangeal joint without articular erosions.

In this situation, articular erosions usually provide convincing evidence for the diagnosis of RA.

In summary, the diagnosis of SLE is based upon the existence of certain clinical features associated with the presence of LE cells or ANA. Other conditions, particularly when specific or curative therapy may be available, must be excluded. Except while receiving corticosteroid or immunosuppressive therapy, the absence of antinuclear antibodies in the presence of active disease excludes the diagnosis of SLE. Pathological features may be helpful, but are not sufficiently available to the clinician. The coexistence of RA with SLE, SLE with erosive arthritis, and RA with glomerulonephritis are all extremely rare. The presence of rheumatoid factor does not protect against the development of glomerulonephritis.

Nuclear Antigens and Antinuclear Antibodies in Lupus Nephritis*

DR. YALE B. BICKEL (Department of Medicine and Harbor General Hospital): Considerable evidence has accrued implying that lupus nephritis and other diffuse glomerular diseases arise as a

consequence of immunologic mechanisms.⁵⁸ Similarities between these disorders and experimentally induced immunologic renal diseases suggest that there are two distinct pathways by which nephritis may develop. In nephrotoxic serum nephritis,⁵³ antiglomerular basement membrane (anti-GBM) antibodies invoke renal injury by combining with antigenic sites on or within the glomerular basement membrane, consuming complement in the reaction. Immunofluorescent studies performed on renal tissue from involved kidneys revealed the presence of linear deposits of immunoglobulins and complement components (beta₂-globulin) along the basement membrane.⁶³ A similar pattern of immunoglobulin deposition may be found in the kidneys of patients with Goodpasture's syndrome²⁴ and chronic progressive glomerulonephritis.

Experimental nephritis may also be produced by the intraglomerular deposition of antigen-antibody complexes.¹⁹ In these instances, immunofluorescent studies reveal the presence of granular or "lumpy-bumpy" deposits of immunoglobulin and complement,¹⁸ corresponding to electron-dense subepithelial deposits within the basement membrane visible by electron microscopy. Morphologically similar findings occur in lupus ne-

*This project was supported in part by a grant from the Southern California Arthritis Foundation.

phritis^{27,46,65} and in post-streptococcal glomerulonephritis,^{1,57} suggesting that in these diseases the kidney is injured as an "innocent bystander" by the deposition of antigen-antibody complexes arising in the circulation.

Antinuclear antibodies reactive with a variety of nuclear antigens may be detected in the sera of virtually all patients with active, untreated SLE.⁶ Although these antibodies exert no direct cytopathic effect when transfused into normal recipients,⁵² on transplacental transfer,¹¹ or when introduced into tissue cultures,⁸⁰ they may participate in immunologic injury by combining with nuclear antigens to form circulating phlogistic complexes capable of depositing within the kidneys. The granular pattern of deposition of immunoglobulins and complement within the basement membrane⁶⁵ and the consistently decreased serum complement level during active stages of nephritis^{25,47,60,79} support this concept. Additional observations in SLE lend further credence to the role of nuclear antigen-ANA complexes in invoking renal injury. It has been shown that the ratio of light chain types within immune deposits in SLE is independent of their serum ratio³⁸ and there is, in general, a correspondence of the classes of bound immunoglobulins to serum titers of each antinuclear immunoglobulin.⁷⁵ These data suggest that glomerular-bound immunoglobulins represent specific antibody globulin deposits rather than immunoglobulins "trapped" from the circulation independent of antibody activity.

ANA's reactive with DNA, nucleoprotein, and phosphate buffer-extractable nuclear antigens have been eluted from isolated glomeruli of lupus kidneys.^{28,32,44,45} *In vivo* localization of ANA to non-viable renal nuclei paralleling the immunopathology of the cutaneous lesions of SLE⁷⁷ cannot account for the presence of these antibodies in eluates from affected kidneys, since such *in vivo* reactions occur only rarely in the kidney.⁶⁵ *In vitro* reaction of serum ANA with nuclear antigens liberated during the isolation of glomeruli likewise does not explain the presence of ANA in such eluates, since quantitative determinations demonstrate higher antibody concentrations expressed in activity per unit of gamma globulin in the eluates compared with corresponding sera.⁴⁴ Other antibodies found in the sera are absent in the eluates, further supporting the belief that there is deposition and concentration of ANA-containing complexes within the glomerular basement membrane.

TABLE 2.—Evidence in Support of the Role of Nuclear Antigen-Antinuclear Antibody Complexes in the Pathogenesis of Nephritis in SLE

1. Immunoglobulins and complement are present in granular immunofluorescent and electron-dense deposits within the basement membrane of affected glomeruli⁶⁵ similar to the findings in serum sickness.¹⁹
2. Acid buffer and molar saline eluates which dissociate antigen-antibody complexes contain antinuclear antibodies in concentrations greater than in corresponding sera.^{28,32,44,45}
3. Eluates from deoxyribonuclease-treated isolated glomeruli contain antinuclear antibodies specific for DNA and nucleoprotein.⁴⁴
4. Serum complement levels are depressed during periods of active nephritis.^{25,47,60,79}
5. DNA antigen has been demonstrated in the serum of some patients with lupus nephritis.⁷⁸
6. DNA and other antigens reactive with ANA-containing serum have been demonstrated by immunofluorescence in the deposits within the glomerular basement membrane.⁴⁴

Unlike many antinuclear antibodies that may be found in the serum of patients with a variety of diseases, antibodies to DNA are most often associated with SLE, especially with active renal disease.⁷¹ They may occasionally occur in chronic active hepatitis and are rarely found in the serum of patients with chronic rheumatoid arthritis.⁹ On the basis of their frequency of occurrence, alterations in titer with variations in disease activity and their specificity for SLE, DNA-anti-DNA complexes have been implicated pathogenetically in lupus nephritis. DNA antigen has been found in the sera of patients with SLE⁷⁸ before the development of an exacerbation of nephritis and when anti-DNA antibody could not be detected. This suggests that DNA-anti-DNA complexes, formed in antigen excess, may have participated in the production of nephritis. The demonstration of anti-DNA and antinucleoprotein antibodies in eluates obtained from isolated glomeruli treated with deoxyribonuclease (DNase) which releases antibody previously complexed to DNA,⁴⁴ further incriminates the DNA-anti-DNA system in the propagation of renal injury.

Immunofluorescent studies using fluorescein-labeled anti-DNA antibodies demonstrated the presence of DNA antigen within the glomerular basement membrane of affected kidneys, corresponding to the localization of gamma globulins.⁴⁴ A summary of the data supporting the role of nuclear antigen-antinuclear antibody complexes in the production of lupus nephritis is presented in Table 2.

In further pursuit of this concept, we have recently performed studies¹⁰ similar to those de-

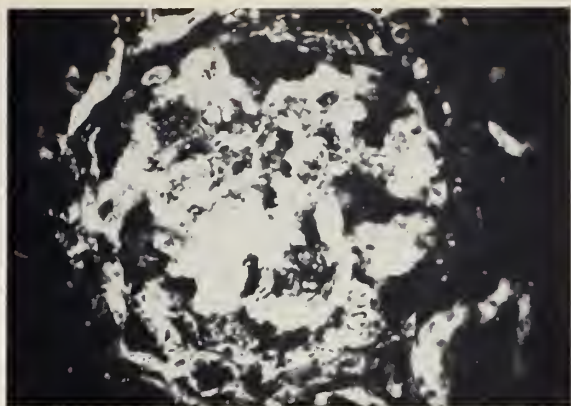


Figure 2.—Section of kidney showing fluorescent granular deposits of immunoglobulin-C within the glomerular basement membrane of SLE kidney ($\times 250$).

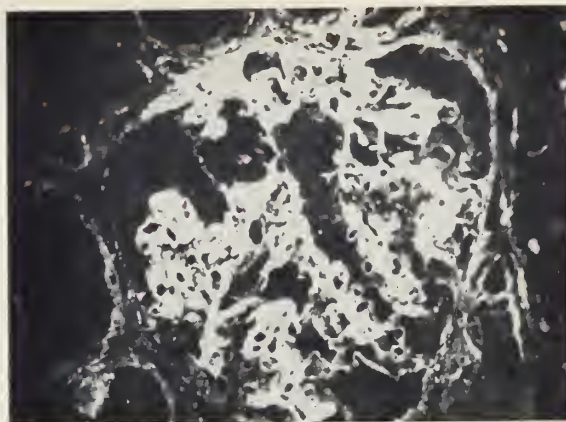


Figure 3.—Glomerulus stained with fluorescein-conjugated rabbit anti-human γ -globulin reveals deposits of complement similar to the localization of immunoglobulin ($\times 250$).

scribed. I should like to present some of these data, which are essentially in accord with previous observations.

Immunofluorescent studies were performed on renal tissue obtained by percutaneous biopsy or at autopsy from patients with lupus nephritis. In all instances, granular deposits of gamma-G globulin and beta γ -globulin were seen within the glomerular basement membrane and occasional blood vessel walls (Figures 2 and 3). Localization of gamma-M was less frequent and corresponded to the location of gamma-G deposits. Fibrinogen, when present, appeared between focal glomerular loops and within occasional crescents. Glomerular localization of albumin did not occur. Subepithelial electron-dense deposits were present in specimens examined by electron microscopy.

In an attempt to characterize the nature of the intraglomerular immunoglobulin deposits, isolated glomeruli of affected kidneys were eluted with acid buffer or concentrated salt solutions and the eluates were tested for the presence of antinuclear, anti-GBM and other antibodies. ANA's demonstrated by indirect immunofluorescence on human leukocytes, were present in the eluates in greater concentrations than in the corresponding sera. Nuclear fluorescence could be abolished by pretreatment of the nuclear substrate with DNase.

We then attempted to confirm the localization of nuclear antigens within the immune deposits by staining the tissue with a reagent antibody (FANA) prepared from an SLE serum containing a high titer of ANA including anti-DNA. Direct staining of human leukocytes revealed bright nuclear fluorescence which was partially abolished by pretreatment with DNase. In order to remove *in vivo* bound

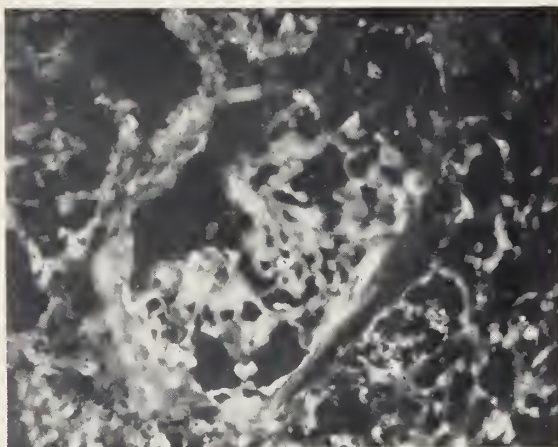


Figure 4.—Staining of uneluted glomerulus by fluorescein-conjugated reagent antibody (see text) reveals bright staining of intrarenal nuclei ($\times 250$).

ANA, "soft" elutions were performed by incubating the tissues with molar saline at intervals varying from 15 minutes to 3 hours, prior to the application of FANA. Controls included blocking experiments with unconjugated reagent antibody. Bright fluorescence of intrarenal nuclei was observed in uneluted specimens (Figure 4), demonstrating the specificity of the FANA for nuclear antigens. Putative nuclear antigens were demonstrated within the GBM deposits of two lupus kidneys which revealed bright granular fluorescence of antigen reactive with the FANA (Figure 5). Application of DNase to the eluted specimen prior to incubation with FANA abolished fluorescence in some glomeruli and not in others, suggesting that DNA is but one of a variety of antigens which, in SLE, may participate in the development of com-



Figure 5.— Fluorescence of putative nuclear antigens seen within the glomerular basement membrane of lupus kidney eluted for 30 minutes and stained with fluorescein-conjugated reagent ANA ($\times 250$).

plex-induced nephritis. Other systems of antibodies and nuclear or cytoplasmic antigens may be involved in the production of lupus nephritis.

In summary, recent investigations have marshalled data implicating immunologic mechanisms in the pathogenesis of lupus nephritis. The causal events resulting in the initiation of these immunologic responses, however, are not known, which provides fertile ground for future investigations.

Serum Cryoprecipitates in Patients With Systemic Lupus Erythematosus

DR. RUNE FORSÉN (Department of Medicine): Cryoprecipitates are frequently found in sera of patients with SLE. Christian and coworkers^{13,34} demonstrated the presence of IgG and IgM immunoglobulins, the 11s component of c'1 complement, and alpha-2 macroglobulin in such precipitates. IgA immunoglobulin and other components of complement were identified in some cases. Precipitation appeared dependent upon the presence of the 11s component and IgM possessing antiglobulin activity. Stastny and Ziff⁷⁴ found that reprecipitation after fractionation could be demonstrated upon recombination of the IgG and 11s components without the IgM fraction. These investigators also found antinuclear activity of the IgG fraction, which appeared to be less per quantity of IgG than the activity demonstrated in the IgG fraction isolated from the corresponding serum. In a study of nine cryoprecipitates, Lee and Rivero⁵⁰ identified the presence of DNA in one case.

The available data have led to speculation as to the possible significance of the cryoprecipi-

tates. An interesting but by no means proven hypothesis is that they may represent circulating immune complexes participating in the genesis of nephritis and other features of the disease.

A study was done on an unselected sample of SLE patients with special attention given to the presence of antinuclear antibodies and DNA in cryoprecipitates. Serum samples were separated at 37°C and refrigerated at 4°C for four days. Cryoprecipitates were isolated and washed four times in cold phosphate-buffered saline solution (pH 7.2). The precipitates were re-suspended in phosphate-buffered saline solution by mechanical disruption and incubation for two hours at 37°C immediately before the various serologic tests. They were incompletely soluble. The identified components and properties of the cryoprecipitates are summarized in Table 3.

Cryoprecipitation occurred in 16 of 18 tested sera from different patients. Precipitated protein was measured by the modified Folin method, showing a range of 31 to 339 μ g of protein precipitated per ml of serum.⁵¹ The presence of IgG, IgA, IgM, and the B₁A/B₁C component of complement were tested for, using a double diffusion method against goat antisera specific for these components and with suspensions containing 0.8 to 8.5 mg cryoprotein per ml.⁶⁴ Quantitation of IgG, IgA and IgM was performed by a radial diffusion method.²⁶ Table 3 contains quantitative values for the immunoglobulin content in those instances where sufficient quantity was present. Cases where their presence was only demonstrated by double diffusion are indicated as positive. IgG and IgM were present in all cryoprecipitates. IgA was identified in 11 of 16, and B₁A/B₁C in 7 of 16 samples.

All cryoprecipitates, both heat-inactivated at 56°C and non-inactivated, showed positive Fraction II latex fixation.³⁰ Because of insufficient material for standardization of concentration, titration was not attempted.

Supernatant sera and cryoprecipitates were specifically tested for the presence of IgG and IgM antinuclear antibodies, using a three-layer immunofluorescent method and a substrate of human leukocytes.⁴ The cryoprotein suspensions used contained 0.4 to 4 mg protein per ml. IgG ANA's were found in 10 of 15 supernatant sera, which were tested undiluted, and in 14 of 15 corresponding cryoprecipitates. This suggests that IgG ANA's may have been concentrated in the precipitates in at least four cases, since the cryoprecipitate sus-

TABLE 3.—Components Identified in Cryoprecipitates from SLE Sera

Patient	Cryoprotein*	IgG*	IgA*	IgM*	B ₁ A/B ₁ C	ANA		Diphenylamine Reaction DNA Equivalent*	Reactivity† Assay for DNA
						IgG	IgM		
J.M.	161	5	+	17	+	+	+	4.1	+
D.W.	80	9	+	23	0	+	+	0	0
C.M.	87	9	+	5	0	+	0	0.3	0
H.M.	122	30	0	13	0	+	+	1.5	0
P.M.	255	32	+	19	0	+	+	0	0
J.G.	55	6	+	21	0	+	+	0	0
B.L.	141	16	5	43	+	+	0	0.5	0
G.T.	339	8	5	21	+	not tested		0	0
M.A.	31	5	0	13	+	+	0	0	0
M.G.	68	6	+	3	+	+	+	1.9	+
B.T.	30	4	0	4	0	+	+	0	0
E.P.	43	6	+	10	0	0	+	0.4	0
B.M.	115	5	8	14	+	+	0	3.4	0
R.A.	71	5	0	+	+	+	+	0.4	0
J.S.	94	22	0	32	0	+	+	0.7	0
C.B.	117	10	1	16	0	+	+	0.5	0

* μ g per ml of serum.

†Reactivity between heat-denatured cryoprecipitate and anti-DNA serum in double diffusion system.

pensions contained considerably less IgG than their corresponding sera. IgM ANA's were apparently demonstrated in 13 of 15 supernatant sera and in 11 of 15 corresponding cryoprecipitates. Since fractionation was not carried out, this may have represented "true" IgM ANA's or an artifact due to IgM antiglobulin attached to IgG ANA's.

The diphenylamine reaction is specific for deoxy sugars.²⁹ Ten of 16 cryoprecipitates were weakly reactive with diphenylamine, a finding of unclear significance, since other substances (such as sialic acid) are also reactive. In order to verify whether this reactivity represented the presence of DNA, the cryoprecipitates were studied in a double diffusion system⁷⁶ against a rabbit serum with specific anti-DNA activity produced by immunization of rabbits with methylated bovine serum albumin-DNA conjugates. These anti-DNA sera do not react with oligonucleotides and they react more readily with heat-denatured than with native DNA. DNA was not demonstrable by this method in the cryoprecipitates when tested in their "native" state. After heat denaturation at 100°C for 10 minutes, however, DNA was demonstrable in two cases (J.M. and B.M., Table 3). Another specimen obtained at a different time from patient J.M. was likewise positive. The fact that precipitin lines did not form in the presence of DNase further verified that the substance identified was DNA.

Our study confirms earlier work showing the constant presence of IgG and IgM in cryoprecipitates from SLE sera; IgA and B₁A/B₁C component of complement were present in some cases. IgG

ANA's were frequently found and appeared to have been selectively precipitated in some cases. This is contradictory to the findings of Stastny and Ziff,⁷⁴ who found less antinuclear activity per quantity of IgG in the cryoprecipitate than in the corresponding serum. These investigators, however, used the separated IgG fraction for this test, while our study employed whole re-suspended cryoprecipitate. The apparent concentration of IgG ANA's in some cases and the presence of DNA in a few cases allows one to speculate that in some instances a nuclear antigen and an antinuclear antibody may constitute a basic immune complex capable of cryoprecipitation with other cofactors. This hypothesis appears promising enough to warrant further work. The currently available data do not allow any clear correlation between the presence and nature of serum cryoprecipitates and clinical aspects to this disease.

Therapy of Lupus Glomerulonephritis

DR. HARVEY GONICK (Department of Medicine): Dr. Bickel has presented a strong case for the argument that the renal lesion in lupus (SLE) nephritis is immunological in origin, due to the deposition of immune complexes with a subsequent inflammatory reaction.

Our interest in the use of the combination of azathioprine and prednisone in the treatment of this potentially lethal disease was stimulated by the relatively good success in treating the rejection reaction in patients receiving renal homografts, as well as by the preliminary experience of

Michael et al⁵⁹ in a pediatric population with immunological renal disease, including five patients who had SLE nephritis.

In order to examine critically the necessity for using cytotoxic drugs in SLE nephritis, it is useful first to review the overall incidence of the renal lesion in lupus as well as some of the available survival figures. Clinically apparent renal disease has been reported to occur in SLE in 46 to 56 percent of all cases.^{22,56,70} Autopsy surveys have indicated that the incidence of renal disease is even higher, ranging from 75 to 100 percent.⁶⁶

In recent years it has become apparent that renal disease is the leading cause of death in SLE. In 1964, Dubois²³ reviewed a personal series of 135 cases and found that 34 percent had died of renal disease. This contrasts with earlier reviews in the preantibiotic era, which indicated that infectious disease was a leading cause of death,⁴³ and in the postantibiotic but presteroid era, when central nervous system disease was a more common cause of death.^{21,36}

In an extensive review by Harvey³⁶ in 1954 of 99 unselected cases of SLE (in which approximately 75 percent of the patients were receiving steroids) it was found that 52 percent of the patients had a four-year survival from the time of diagnosis. In 1956 Dubois²¹ analyzed 163 cases of SLE dated from the first appearance of symptoms. His figures indicate a 50 percent five-year survival term on adequate treatment, but only a 50 percent two-year survival on "inadequate treatment," that is, a steroid dose of less than the equivalent of 200 mg of cortisone per day. A review by Meislin and Rothfield⁵⁶ in 1968 of 200 cases of adult-onset SLE indicated half of this group had clinically demonstrable renal disease but nevertheless had a 50 percent 20-year survival, whereas the half without clinical renal disease had a 70 percent 20-year survival. These differences in survival rates in several series are difficult to reconcile, but may relate to the severity of the renal lesion. When overt renal disease supervenes, features of ominous prognostic import include the nephrotic syndrome,^{67,73} azotemia of even mild degree,⁶⁷ and diffuse proliferative glomerular involvement.⁷⁰

Adrenal steroids are frequently effective in treating patients who are acutely ill with active SLE, but their role in established nephropathy is controversial. Early experience^{55,73} suggested that steroids were ineffective in nephritis despite suppression of active disease in other systems. Pollak and

TABLE 4.—Protocol for Prednisone-Azathioprine Study

1. Evaluation of effect of combined therapy on patients with SLE nephritis or steroid-resistant nephrotic syndrome associated with glomerulonephritis.
2. Serial study of renal function, morphology and immunological parameters as indices of response to therapy.
3. Azathioprine dosage: 2 to 4 mg per kg daily.
Prednisone dosage: 30 to 60 mg daily in SLE; 60 mg q.o.d. in nephrotic syndrome.

coworkers⁶⁷ observed no consistent correlation between renal and extrarenal activity, but demonstrated improvement and decreased mortality in SLE glomerulonephritis treated with prednisone in high dose (40 to 60 mg daily) for a period of 6 months. These results were looked upon as an improvement over earlier experience of this group with low-dose steroid therapy, that is, the amount sufficient to suppress systemic manifestations of the disease but not sufficient to suppress the renal lesion. This suggestion has been challenged by several subsequent studies, notably a cooperative study headed by Christian,⁴⁰ in which an unbiased comparison of high-dose and low-dose steroid therapy indicated no significant difference between these two treatment regimens.

The histologic features of SLE nephritis have been carefully analyzed by Muehrcke et al⁶¹ and recently reviewed by Comerford and Cohen.¹⁴ Active glomerular lesions include cellular proliferation, wire loops, fibrinoid necrosis, hyaline thrombi, and hematoxyphil bodies. Interstitial abnormalities generally reflect the extent of glomerular damage. Clinical improvement is often accompanied by a corresponding decrease in histological activity.⁶⁷ Both adrenal steroids^{67,72} and cytotoxic agents⁵⁹ appear to reduce the cellular component of the glomerular response in SLE, but basement membrane abnormalities are frequently unchanged.

Table 4 indicates the protocol we have used in following patients with immunological renal disease. Our intent was to study the effect of combined therapy (that is, azathioprine and prednisone) in patients with SLE and glomerulonephritis with steroid-resistant nephrotic syndrome. All patients had serial studies of renal function, morphology and immunology following therapy. Percutaneous renal biopsy was performed before treatment was begun, and was repeated at 6-month intervals. Biopsy specimens were divided for light and immunofluorescent microscopy. Glomeruli were stained for IgG, the beta ₁C-globulin component of complement, and fibrinogen. Changes in

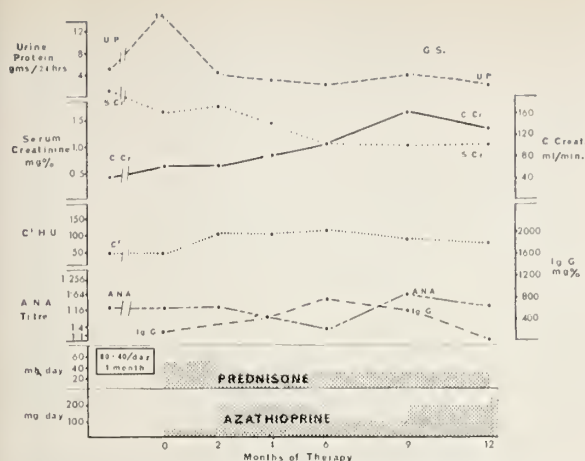


Chart 2.—Clinical course of patient G.S. (Table 5) following treatment with prednisone and azathioprine.

light and immunofluorescent specimens were graded on a semi-quantitative basis for later analysis. Renal function studies included measurements of creatinine clearance, ^{125}I -iodothalamate clearance, urine protein excretion, and Addis counts. Immunological studies included ANA, quantitative immunoglobulins, total serum hemolytic complement (C'), and beta $_{1\text{C}}$ -globulin ($\text{C}'3$). The functional and immunological studies were performed before therapy was begun and then at 2- to 4-week intervals. Azathioprine was used in a dose of 2 to 4 mg daily, more commonly in the lower dose range. Patients with lupus were treated with 30 to 60 mg of prednisone daily, whereas patients with glomerulonephritis were treated with 60 mg every other day.

Chart 2 indicates the clinical course in a typical patient, this one a 17-year-old Caucasian male who presented with a 4-month history of fever, arthralgias, hypertension, and anasarca due to severe nephrotic syndrome. He had not responded to prednisone in a dose range of 40 to 80 mg per day for one month before the initiation of combined therapy. Within 6 months there was a decided clinical improvement associated with a rise in glomerular filtration rate and reduction in proteinuria. Serum complement rose to normal and ANA titers fell (but rose again subsequently despite continued clinical improvement). Pretreatment biopsy showed severe, diffuse membrano-proliferative glomerulonephritis with some localized necrosis. Immunofluorescence revealed a typical granular deposition of IgG and beta $_{1\text{C}}$ along the glomerular capillary membranes. Following treatment there was pronounced diminution in the pro-

liferative changes as well as in the amount of IgG and beta $_{1\text{C}}$ deposition.

Table 5 lists the overall results obtained in 14 patients with SLE who had been on treatment for at least 6 months as of June 1968. It should be emphasized that two of these patients (N.M. and S.B.) had severe azotemia with creatinine clearances of 10 and 12 ml/min. Since four other patients had mild azotemia, it is apparent that we are dealing with a group which would be expected to have a poor prognosis. In addition, nine patients were nephrotic, again a poor prognostic sign.

Serum complement was depressed in eight of twelve patients before therapy and rose in seven of these eight following therapy, correlating relatively well with functional and/or morphologic improvement. ANA titer, on the other hand, was low or even absent in four patients with biopsy-proved glomerulitis. When initially elevated, ANA titer usually fell, but the decrease did not correlate with changes in functional measurements. Immunoglobulin-G levels were unpredictable. Some patients with relatively low values had heavy proteinuria and it is possible that they were losing large quantities of immunoglobulins in the urine. Subsequent data, however, have demonstrated that IgG synthesis is depressed by azathioprine.* When IgG levels before therapy were elevated, successful treatment was usually associated with a fall in IgG to normal. Immunofluorescence frequently decreased, but there was not always a good correlation between diminution in immunofluorescence and other gauges of progress. Histologically, the most impressive change was a decrease in glomerular cellular proliferation, seen in 10 of 14 patients.

Complications were relatively frequent on combined therapy (Table 6). Two patients died of infections, one from Gram-negative sepsis following deep abscesses of thighs and buttocks, and one from subarachnoid hemorrhage incident to probable bacterial meningitis. Hypercorticism appeared in 12 patients, while hyperglycemia developed in three and three others became emotionally disturbed. Hepatotoxicity was not seen in these lupus cases but has been noted in patients with glomerulonephritis and nephrotic syndrome treated on a similar protocol.

In summary, it would appear that the combination of azathioprine and prednisone is a promising

*Levy, J., Barnett, E. V., McDonald, N. S., and Klinenberg, J. R.: Reduced IgG and IgM synthesis with azathioprine therapy, *Arthritis Rheum.*, Dec. 1969, in press (abstract).

TABLE 5.—Results of Combined Therapy in SLE Nephritis

Patient	GFR	Urine Protein	ANA	C'	IgG	Pathology (Proliferation)	Immunofluorescence	Months Rx
V.S.	inc.	dec.	dec.	inc.	dec.	n.c.	dec.	12
H.K.	inc.	dec.	dec.	n	dec.	dec.	dec.	12
N.A.	n.c.	dec.	dec.	inc.	..	dec.	dec.	21
D.M.	inc.	dec.	n.c.	low— n.c.	inc.	dec.	dec.	12
M.A.	inc.	dec.	dec.	inc.	inc.	dec.	dec.	6
E.S.*	dec.	dec.	dec.	inc.	dec.	n.c.	dec.	6
E.P.	inc.	dec.	dec.	inc.	inc.	dec.	..	6
A.B.	n.c.	dec.	dec.	dec.	..	27
G.S.	inc.	dec.	dec.	inc.	inc.	dec.	dec.	13
N.M.	dec.	n.c.	dec.	dec.	..	30
R.A.	n.c.	dec.	n.c.	n	n.c.	n.c.	n.c.	6
R.G.*	n.c.	inc.	n.c.	inc.	dec.	n.c.	inc.	12
N.M.†	n.c.	n.c.	n	n	n.c.	dec.	inc.	7
S.B.†	dec.	n.c.	dec.	n	n.c.	dec.	..	7

Inc.: Increased; Dec.: Decreased; n.c.: No change; n: Normal.

*Died of infection. †Died of uremia.

TABLE 6.—Complications of Combined Therapy

Total number of patients on Rx	14
Hypertension	12
Infections	4
Hyperglycemia	3
Mental disturbances	3

means of therapy in patients with lupus nephritis, but is not without hazard. A definitive evaluation of the role of this drug combination, however, requires more prolonged observation as well as comparison of effectiveness and toxicity with a matched series of patients treated with each drug independently.

Discussion

DR. BARNETT: What have we accomplished in our attempts to define the cause and cure of diseases in a group of patients that we have labeled as having systemic lupus erythematosus? We have obviously not found the cause or cure as yet. We have spun off a great deal of information of scientific import and we have trained a number of scientists in the attempt.

From Dr. Kantor's presentation it is apparent that we can distinguish systemic lupus erythematosus in certain patients from rheumatoid arthritis in other patients who have similar serologic abnormalities and similar clinical manifestations. On the one hand, SLE patients frequently have glomerulonephritis and rarely have articular erosions, while RA patients show the converse. In our experience, this is a more important distinction than any serologic test. We do know, however, that in

untreated patients the absence of antinuclear antibodies practically excludes the diagnosis of systemic lupus erythematosus.

Dr. Bickel has reviewed the evidence incriminating immune complexes in glomerulonephritis. Our work² has made us particularly receptive to the hypothesis that "nuclear" antigens and antinuclear antibodies participate in such complexes. However, the evidence accumulated so far is too scanty and there are still too many gaps and contradictions. Nuclear antigens in small amounts are present in normal sera.^{3,7} Circulating complexes have been detected without associated glomerulonephritis or hypocomplementemia and the role of DNase and DNase inhibitors is unclear. Current investigations at many centers promise to clarify the matter.

As was suggested by Dr. Forsén, the presence of cryoglobulins may be an indication of circulating complexes. Antigens and antibodies when mixed *in vitro* will precipitate much better at reduced temperatures. This may explain what happens when we place a patient's serum in the refrigerator for 4 days and obtain a precipitate containing a variety of ingredients. Dr. Gonick reviewed our experience in the therapy of lupus glomerulonephritis with combinations of prednisone and azathioprine. Does such a therapeutic trial give us insight into the cause of the disease or its pathogenesis? Since these drugs have multiple pharmacologic actions, such insight has not been forthcoming. These drugs are "anti-inflammatory"; they affect cells that invade the lesion; they affect antibody production; they are antiviral agents and affect the mediators of inflammation.

The Etiologic Significance of Similar Abnormalities in Diseases of Man, Mink, and Mouse

If there are similar abnormalities in diseases of man and of lower species, what interpretation can be made? The serologist studying human disease is frequently confused by the similar abnormalities in tertiary syphilis, leprosy, and subacute bacterial endocarditis. These are human diseases of known and divergent cause, but the serologic similarities apparently reflect similar pathogenetic mechanisms.

Aleutian minks are of a strain developed because of its attractive metallic blue pelt. It was found that such minks of genotype Aa did not reach adult life but died with hepatitis, vasculitis, glomerulonephritis and hyperglobulinemia, and some even with monoclonal spikes resembling myeloma proteins.⁶⁸ To complicate matters, it was found that this disease could be transmitted by ultrafiltered material, less than 50 m μ in size, to minks of other strains, to the heterozygotic Aa minks, and even to ferrets.⁴² The veterinarians were thus confronted with an economically important disease that appeared immunologic on the one hand, and infectious on the other.

We were pleased to have the opportunity to study the sera of heterozygotic Aa minks that acquire the disease spontaneously and only late in life.⁸ These Aa minks were given ultrafiltrates of highly infectious spleen material, and 10 weeks later 100 percent had evident disease. We were sent serum specimens before the inoculation of the infectious material, and serum specimens collected 10 weeks later in the presence of obvious disease. Utilizing the sorts of antisera described by Dr. Forsén, we could find antigen in small amounts and low incidence in sera before the development of Aleutian disease (Table 7) and in large amounts and higher incidence in the presence of Aleutian disease. ANA's detectable by immunodiffusion, precipitin tests in dilute agarose with single-strand calf thymus DNA were detected only in sera from minks with overt disease. ANA's detectable by the more sensitive immunofluorescence technique using human leukocyte nuclei as antigens were detected before overt disease developed, but were detectable in higher titer and greater incidence in the presence of the disease.

Sera were collected from Aa minks that acquired the disease spontaneously in later life. They had

TABLE 7.—Incidence of "Nuclear" Antigen and Antinuclear Antibodies in Experimentally Induced Aleutian Disease (AD)

	Pre-AD* Percent	Post-AD† Percent
Antigen content by precipitin tests	38	50
ANA by precipitin tests	0	95
ANA by immunofluorescence	35	100

*Sera obtained before disease.

†Sera obtained at time of evident disease.

large amounts of antigens detectable by anti-DNA antibodies and they had a high incidence of antibody to single strand DNA. Aa minks from different mink farms with low incidence of spontaneous Aleutian disease but with the same genetic susceptibility to this disease did not show these abnormalities.

The results of our studies on the sera of New Zealand black (NZB) mice were very similar to the results obtained with Aleutian mink sera. New Zealand black mice are well known to have a high incidence of hypergammaglobulinemia, hemolytic anemia, nephritis and antinuclear antibodies. We recently demonstrated that sera from these mice have a high incidence of precipitating antibodies to single-strand calf thymus DNA, and nuclear antigens are frequently demonstrable as well.⁸¹

The antigens found in sera from persons with SLE, from minks with Aleutian disease, and from NZB mice can be detected by a variety of anti-DNA antibodies (Table 8).⁸¹ In some cases the nuclear antigens appear resistant to DNase. Since the immunodiffusion studies demonstrate that the nuclear antigens show either complete or partial identity with single-strand calf thymus DNA, they apparently have purine and pyrimidine determinants. The relative resistance to DNase may be attributable to the binding of the antigens by ANA present in the specimens.

Our immunodiffusion studies to date make it appear unlikely that the nuclear antigens in these three conditions are identical.

Antinuclear antibodies are found in all three situations. Among these ANA's we have consistently detected antibodies to single-strand DNA. Does this suggest that the primary immunogen in these three situations is a "denatured" DNA or single-strand DNA virus? In all three situations there is hypergammaglobulinemia, vasculitis and nephritis. In systemic lupus erythematosus there is mild arthritis, and in all three conditions the role of immune complexes in pathogenesis has been in-

TABLE 8.—Comparison of Systemic Lupus Erythematosus, Aleutian Disease and the Disease in NZB Mice

Factor	SLE	AD	NZB
"Nuclear" antigens in sera	rare	frequent	rare
Antinuclear antibodies	frequent	frequent	frequent
Antibodies to SS DNA	frequent	frequent	frequent
Hyperglobulinemia	frequent	frequent	frequent
Vasculitis	frequent	frequent	frequent
Nephritis	frequent	frequent	frequent
Arthritis	mild	absent	absent
Role of immune complexes in pathogenesis	incriminated	incriminated	incriminated
Infectious	?	yes	in controversy
Genetic factors	in controversy	present	present

criminated.⁵ Persistent infections of mice with lymphocytic choriomeningitis virus or lactic dehydrogenase virus has been associated with immune complex disease with these clinical characteristics. The prevalence of antibodies to single-strand DNA in SLE, Aleutian minks and mice has encouraged us to pursue serologic studies on the possible role of small DNA-containing viruses (picodnaviruses).^{5,54}

That Aleutian disease is caused by an infectious process appears well documented by the transmittability of the disease by ultrafiltrates. This may also be the case for the disease in NZB mice. Surprising electron microscopic observations⁶² recently have been added to evidence that systemic lupus erythematosus is of viral origin. The susceptibility of certain strains of minks and mice indicates genetic predisposition to the infectious agent. Epidemiologic studies in SLE are also consistent with the combination of genetic susceptibility plus an inciting agent.

It is particularly uncomfortable for scientists experienced in data collection from well controlled experiments to deal with data suggesting multifactorial etiologic agents. The clinical investigator studying systemic lupus erythematosus must now consider the possible interrelationships of autoimmunity, immune complex disease, persistent infection and genetic susceptibility.

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EDITORIAL

Medicine and the 1970s

MEDICINE ALONG WITH THE NATION and the world is about to enter a new decade. It seems certain that the 1970s will be at least as shattering to tradition as were the 1960s. There is bound to be change and much of it fundamental. Depending upon one's outlook what lies ahead may be viewed with anticipation or foreboding, or perhaps a little of each.

The decade now just closing has seen widespread challenge to and even rejection of many of the traditional attitudes and values which have long been bulwarks of American and indeed Western society. There have been substantial inroads upon long accepted standards of public and private morality as this nation has hitherto understood them. The established order of many churches, the military and even the law has been more or less successfully attacked. The educational system, both public and private, has been exposed as curiously vulnerable to intellectual and physical confrontation and surprisingly ill-fitted for adaptation or change.

Medicine has by no means escaped criticism. The established approach to health care delivery was all but shattered during the 1960s by far-reaching federal legislation. The medical profession was singled out for particular attack and vilification in the press and elsewhere, and at the end of the decade remains a convenient whipping boy. But in spite of all the attacks and public

abuse heaped upon the profession, the public opinion polls continue to indicate that physicians and even organized medicine stand very high in the public esteem. Perhaps this in part at least reflects the dramatic achievements of medical science. In any case the thrust of the attack on health care was not so much to tear down as to try to create something better.

The 1970s will surely be different. Some way will be found to end the kinds of disorder and destruction which in the long run cannot be tolerated by any society, especially when those who are tearing things down have nothing to propose. There will be new values which will find acceptance to replace those which are being rejected. There is much to suggest that at least some of these new values will be based upon what is known of human biology, that is, the realities of human nature and human behavior. This will occur as modern society inevitably comes to grips with what must be done to achieve health and well-being for individual citizens and indeed all of the humanity encased in this closed and seemingly shrinking biosphere from which there is no practical escape either now or in the future.

It is entirely possible that the 1970s will mark the beginning of a new cultural recognition of the biologic nature of human society in much the same way that the biologic nature of man himself was finally recognized toward the end of the last century. Medicine, which applies what is known in the human biology of health and disease to promote health, well-being and survival not only of the individual but of the species, should have an important and exciting role to play. Physicians may look to the 1970s with anticipation, certainly not foreboding. We may well be at the threshold of a new era in the history of human society.

sponses damage host tissue and produce disease. These two phenomena suggest that what would be expected to be harmful may be helpful in certain circumstances, and vice versa. Furthermore, states of immunological sensitivity and tolerance can co-exist in the same animal, with first one and then the other predominating. The immune response of the whole animal is malleable. The implications of this flexibility as it affects the intensity, quality, and reversibility of immune responses are only beginning to be understood.

The conference from UCLA on Systemic Lupus Erythematosus, published in this issue, illustrates many recent advances and underscores many current problems in clinical immunology. It is now possible to identify multiple variations of the classical clinical categories of rheumatic disease and to observe one evolve into another. It is also possible to identify specific immunological events accompanying certain types of disease, such as the association of autoantibody to DNA with nephritis. The converse association, involving the protective effect of certain autoantibodies, has also been established in experimental disease and suggested in SLE. In experimental animals, analogues of autoimmune hemolytic anemia and SLE arise naturally in strains with particular genotypes as a product of aging or possibly viral infection.

We still do not understand, however, the associations of particular serological abnormalities with patterns of clinical disease, the variations in serological patterns which accompany transformation of one clinical form into another, or even the natural history of most variants of SLE. We have only very modest knowledge of the mechanisms of tissue damage. It remains very difficult to establish an appropriate prognosis for individual patients or to decide with accuracy the type and intensity of treatment which is needed.

The current treatment of immunological diseases further emphasizes our ignorance. Corticosteroids have enjoyed widespread use in the treatment of these diseases since the early 1950s. Experience establishes beyond doubt that they can terminate the lupus crisis. However, there still does not exist a single controlled study demonstrating conclusively the benefit of these agents. Their comparative utility in different forms of SLE and related diseases is also unresolved. Recently it has become popular to use cytotoxic agents, particularly in the treatment of patients who appear resistant to corticosteroids. The rationale is sound: Cytotoxic agents

Systemic Lupus Erythematosus

FOR OVER HALF A CENTURY systemic lupus erythematosus (SLE) was considered a rare and fatal disease. During the 1930s suspicions arose that hypersensitivity might be involved in pathogenesis. In 1948 the LE cell was discovered. In the 1950s the application of immunological techniques in the study of SLE led to the identification of autoimmunity in man, and established that the formation of LE cells is an immunological event. In succeeding years the use of diagnostic immunological techniques has led to the recognition of an extraordinarily broad spectrum of clinical forms of SLE affecting many different major organ systems with intensities from mild to fulminating.

During the same period, the discipline of immunology has rapidly matured. Transplantation immunology has emerged, and with it a recognition of the phenomenon of immunological tolerance which is a state of unresponsiveness to antigen antithetical to classical sensitivity. The cellular events which constitute the immune response have at least in part been identified and thereby the sequential components of that response have been opened for study. Much of the molecular structure of antibody is now known. The role of individual genotype in governing the immune response is being established. Autoimmunity has become a recognized component of diseases in fields as previously separate as Rheumatology, Endocrinology, Gastroenterology, and Neurology.

Matters have progressed further. It is now well established that autoantibodies to a tissue can in certain instances protect that tissue from immunologically induced disease. Certain types of viral infections are apparently harmless until host defenses come into play; then the cellular protection re-

inhibit the primary immune response, reduce the secondary response, interfere with cellular hypersensitivity, diminish inflammatory reactions, facilitate the induction of immunological tolerance in certain settings and impede the development of experimental immunological disease. However, the clinical literature on the use of these agents contains only reports of treatment of small numbers of patients and uncontrolled evaluations. Some clinical evidence has been presented suggesting that a combination of corticosteroids and cytotoxic agents is superior to either type of agent alone, but here too the data are not rigorous. Preliminary controlled investigations suggest that the cytotoxic drugs alone are often ineffective in influencing immunological disease. Furthermore the price paid by patients receiving combined therapy is very high in terms of opportunistic infections which have become a frequent cause of serious morbidity and death.

The discussion from UCLA serves to emphasize the needs for the next few years. These include careful clinical observations (1) to establish the natural history of various forms of SLE, (2) to identify rigorously the patterns and significance of different serological reactions in relation to pathogenesis, prognosis and response to therapy and (3) to determine the efficacy of various treatment programs. The influence of patient genotype and of viral infection on susceptibility to immunological disease requires definition. Study of mechanisms of tissue damage may be difficult in man but animal models now provide appropriate subjects for investigation. It should be possible, once these mechanisms are identified, to design specific therapeutic programs to counteract them. The flexibility and adaptability in the immune response make such therapeutic manipulations more than a distant hope; if autoimmunity results from a loss of natural tolerance, perhaps we can discover biological ways to reestablish that tolerance.

The conceptual and methodological tools are at hand to accomplish these objectives. In the past, the study of human disease has provided a great portion of the impetus for the growth of the discipline of immunology. We may hope that more rigorous study of human disease will now yield both improved care of patients and an even greater increment in knowledge of the human immune response.

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Polymyalgia Rheumatica

AMERICAN PHYSICIANS have been slower than those in Britain to accept polymyalgia rheumatica as a distinct clinical syndrome. Perhaps it is less common in North America than in Europe. Nevertheless, once a case is recognized others seem to appear and the incidence may not differ greatly on the two sides of the Atlantic Ocean. In any event, the incidence if it be different has not attracted the attention of epidemiologists.

A more immediate problem, because it has important clinical implications, is the relationship of polymyalgia rheumatica to the syndrome of giant cell arteritis. That name is slowly gaining favor over the terms *temporal* or *cranial* arteritis because it is clear that on occasion the disease can affect any part of the aorta or its branches.

There is general agreement that the musculoskeletal symptomatology of polymyalgia rheumatica and giant cell arteritis is the same and that patients ultimately proven to have giant cell arteritis may have a prodrome of polymyalgia for several years before arterial changes become evident.¹ Unfortunately, it has been well documented that blindness or a serious cerebrovascular accident may be the first manifestation of the arteritis.²

Both polymyalgia rheumatica and giant cell arteritis are dramatically improved by corticosteroid therapy. So striking is the response of the former, even to small doses, that the therapeutic effect has been proposed as a diagnostic test. Larger amounts, however, may be required to control the manifestations of giant cell arteritis, and the frequency of complications, especially osteoporosis in the elderly population characteristically affected, becomes a major concern.

Both diseases tend to have self-limited courses extending over a few months to a year or two, but relapses may occur³ and there is no established means of knowing when therapy can be stopped. The author knows of three patients with temporal

arteritis who have suffered vertebral compression fractures while on therapy, in one case after only a few months of treatment and in another after attempts over 2 years to reduce the dose of steroid had been frustrated by the reappearance of symptoms. One is, therefore, reluctant to accept immediately the recommendation that since any patient with symptoms of polymyalgia rheumatica may develop serious manifestations of giant cell arteritis, all should be treated with corticosteroid from the outset. This recommendation obviously depends on the supposition that all patients with polymyalgia rheumatica either have giant cell arteritis from the start or are in danger of developing arteritis. It is agreed that the musculoskeletal symptoms are indistinguishable. Muscle biopsy usually shows no pathology,⁴ the vessels involved by giant cell arteritis being larger than those found in muscle. Another approach has been to perform routine temporal artery biopsy when the diagnosis of polymyalgia rheumatica is made. The procedure is a benign one and is certainly indicated when the temporal arteries are found to be tender or thickened and pulseless. However, biopsy specimens showing active or healed temporal arteritis have been obtained from arteries which were clinically normal.

Temporal arteriography has recently been proposed as a better screening procedure and should certainly help to define the area from which to take specimens for biopsy.⁵ It is a fact, unfortunately, that in some patients who develop catastrophic consequences of giant cell arteritis the temporal arteries are never involved.

An autopsy study of the temporal arteries of 39 elderly persons without recorded symptoms of polymyalgia rheumatica or giant cell arteritis demonstrated lesions consistent with healed arteritis in two.⁶ Moreover, both died possibly as a result of arteritis. If carried to the extreme, an argument could be made for investigating the temporal arteries of all elderly persons and at least anyone found on questioning to have fatigue, muscle soreness, headache or any of the vague symptoms which may be a part of the syndromes under discussion. Clearly some middle ground must be found. The absence of normal pulsation in a temporal artery is certainly not conclusive evidence that it is affected by giant cell arteritis, for pulsation may be absent in one or both arteries in 5 percent of middle aged and elderly adults attending an arthritis clinic.⁷

In the final analysis, most physicians would administer corticosteroids to patients with polymyalgia rheumatica who developed headaches, face or scalp pain, or cerebrovascular symptoms of any kind with or without a positive biopsy or arteriogram. Those who do not have such symptoms should probably have one or another procedure performed to demonstrate giant cell arteritis and should be treated if the result is abnormal, whatever the clinical symptoms.

As for the remainder, the physician must be prepared to make a somewhat arbitrary decision based on whatever evidence he finds compelling. Some patients cannot be freed of their disabling muscular complaints by anything other than corticosteroid. The situation is not an unfamiliar one in medicine.

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Whither Nursing?

THE DICTIONARY defines a nurse as "a person skilled in caring for and waiting upon the infirm, the injured, or the sick; specifically: one especially trained to carry out such duties under the supervision of a physician."* Thousands of young girls, and some young men, have been drawn to a career in nursing by this ideal of personal service, under competent direction, to someone who is afflicted or

*Webster's Third New International Dictionary of the English Language—Unabridged.

suffering. Nurses and physicians have thus shared similar attitudes and have worked closely together as a team. The nursing profession has traditionally been held in a kind of preferred status by physicians. The atmosphere has usually been peaceful and much of the time the relationship idyllic.

Recently there are signs that things have begun to change. The traditional more or less all-purpose nurse who at once served as assistant to a physician and attendant to a sick patient has begun to undergo differentiation and she now performs a myriad of specialized functions which may have little or nothing to do with "waiting upon the infirm, the injured, or the sick, under the supervision of a physician." Already there are surgical, psychiatric, intensive care, public health, coronary care, school, office, and administrative nurses, all with special skills. The varieties of nurse specialists are growing in number and importance. Increasingly many of these specialized nurses are being expected to make independent decisions affecting the care of patients, decisions which often must be made in situations quite remote from the immediate supervision of a physician, if indeed there is a supervising physician.

One important and perhaps inevitable result of this specialization is that the nurse has started to drift away from her role as attendant to the patient and has begun to stand more closely with the physician as an assistant, associate or even colleague. As a consequence of this, traditional nursing with its traditional satisfactions is being more and more left to others while the nurse in her new role has yet to be fully accepted as an actual colleague of the physician.

Perhaps this trend may be a root cause of some of the things that are now happening in nursing. But whatever the cause, there are clear signs of some kind of an identity crisis in the nursing profession. We see nursing leadership making very considerable efforts to identify and define what is now to be the role of nursing. There seems to be a driving compulsion to upgrade the status of nursing. The recent bold use of strike tactics with the tacit assistance if not the formal support of a well-known and powerful labor union was considered by many to be very much out of character for this gentle and beloved profession.

It seems more than likely that storm signals will appear along the course upon which nursing is embarked. It is suggested that certain apparent fallacies will lead to some difficulties. For exam-

ple, it seems inconsistent to promote the professionalization of nursing on the one hand and on the other to use tactics which in the view of many serve only to deprofessionalize it. It seems unrealistic to expect to retain the role of bedside nurse and at the same time price the services of a registered nurse substantially beyond what patients can afford in ordinary circumstances. And one may question the ultimate result of what seems to be the efforts of the nursing leadership to create an artificial new administrative role for the nurse in the health care delivery system (particularly in the hospital setting), to force the acceptance of that role by the use of pressure, and then expect the health care economy to support it with some generosity. This appears to be what is occurring, as nearly as one can glean from a perusal of the recent nursing literature and from a rather careful observation of recent strike tactics employed by the nursing profession in California. If this assessment is anywhere near accurate there will not only be storm signals but some quite heavy weather ahead.

If the problem can correctly be viewed as fundamentally an identity crisis, then it should be dealt with as quickly and reasonably as possible. Perhaps the time has come to admit that the specialized registered nurse of today and tomorrow really will no longer be a nurse in the traditional sense, and will more than likely be lifted out of the traditional nursing role to take her place among a new order of physician assistants or physician associates. Perhaps medical associates would be a better term. The need for such an order of well trained health personnel with various and differing skills is becoming increasingly apparent. So far there has been little discussion of the nature of such a new order, but clearly old-fashioned nursing would not be its dominant concern. This new category of professional specialists should stand closely with the physician and share his responsibilities for patient care and for community, environmental and species health care. Men would play an equal role with women. Those who achieved this new status might become recognized as "professional associates in medicine" or given some similar designation commensurate with their training and responsibilities within what is now coming to be called the health team. Traditional nursing would then be left to the new categories of nurses who are already beginning to occupy the field.

Perhaps this will be an answer to "whither nursing?"

A Medical Corpsmen Project

JOSEPH F. DONOVAN, *San Jose*

DURING THE PAST FOUR YEARS reports have been issued dealing with localized, limited projects aimed at utilizing the skills of recently released military medical corpsmen. Only one of these efforts involved the use or extended training of more than a dozen or so men in any one endeavor. At the same time, public statements were being made to the effect that "more than 30,000 such corpsmen" were coming out of the service each year, yet there was little evidence that many of them were being employed in the general private sector for health care services. Questions were constantly being raised in numerous sections of Washington, D.C., regarding "the loss of these men to the health field," methods for recruitment, skills evaluation and employability.

Because of the attention that officers of the Santa Clara County Medical Society had attained in mid-1968 regarding their concerted efforts for a full-scale, community-wide, health manpower utilization program in Santa Clara County, conferences regarding a special military manpower project were initiated by the U.S. Department of Labor.

As a result the Santa Clara County Medical Society entered into a contract with the U.S. Department of Labor (Grant Number 92-05-68-10) as the fiscal agent and administrative arm of the Allied Health Manpower Council of Santa Clara County for the execution of a special military corpsmen study. The goal of the first year was to do a number of things for at least 50 armed services medical corpsmen, but primarily to:

- Provide these discharges with counseling ser-

vices by referral and direct contact with representatives of local health and education agencies;

- Evaluate the individual skills of the discharges and identify training or educational needs to bring him or her up to a level of gainful employment;

- Work with all local health and educational institutions, to arrange for training or job placement or both;

- Work with appropriate state and local agencies to modify licensing procedures or to create "certifications" to permit utilization of these trained discharges.

The California Department of Veterans Affairs reports that 6,000 to 7,000 of these corpsmen released annually return to their home state of California each year. Using a ratio that is applicable to Santa Clara County, as it relates to state population, this would mean that approximately 600 return to Santa Clara County each year, a rate of 50 per month. With such totals from which to work, it seemed that our initial goal of 50 for the first 12 months could be easily achieved. We did not find it so.

In the first 9 months, the Manpower Council was able to process data and make specific contacts, in person or by telephone or correspondence, with 73 released or unreleased medical corpsmen. These were located in the geographical triangle encompassing the territory from downtown San Jose, to downtown Saigon, to shipboard on a Navy vessel in the Bering Sea. The cases are documented.

Project REMED

Project REMED is a nationwide program to give discharged military medical men and women an opportunity to fill critical shortages in civilian

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health occupations. Project REMED has been in operation since January 1968 and is the outgrowth of active cooperation and participation between the departments of Defense, of Labor, of Health, Education, and Welfare, and the Veterans Administration and the American Hospital Association.

Project REMED aims at identification, recruitment, retraining and re-employment of military medical personnel in civilian health occupations. It hopes to identify job opportunities and training or educational opportunities to upgrade abilities of military medical people to meet these needs. The Santa Clara Council expected to make valuable use of REMED.

Project REMED works in this way: at separation centers, each veteran fills out a form developed by the Veterans Employment Service of the U.S. Employment Service which asks his military occupation and skill. A copy is sent to the local office of the State Employment Service closest to the veteran's home. This office endeavors to contact each such veteran, offering a personal interview with the object of placing him in a job or referring him to an educational or training program in the health field. Veterans are urged to contact the employment office if it does not contact them.

The theory of the program is before they are separated from the Armed Forces, men and women will be informed about all of these benefits and will be provided with an outline of the opportunity in the private health field to continue their military occupation experiences. Although there is only scant statistical data, the theory apparently is not working—there have been only 19 such applications in Washington, D.C., and 23 in St. Paul, Minnesota. The office of REMED, in a recently released report, gives five reasons why the program must be restructured or strengthened. Four of the reasons relate to licensure, salary ranges, and state examinations, but the prime one centers on the fact that the contact of such corpsmen at the date of discharge is far too late to direct him effectively to the opportunities in private health fields. In light of these conditions a new tack was taken in the recruitment program in Santa Clara County.

It is recognized that new and realistic evaluation must be made of the compensation levels for new kinds of health workers, particularly in relation to the compensation of existing licensed health professions, before great numbers of potential employees can be enticed into the health services fields.

The Allied Health Manpower Council of Santa Clara County

Although the local U.S. Department of Labor contract for assisting released medical corpsmen is officially with the Santa Clara County Medical Society, the Society has carried on this function through the mechanism of a volunteer community group (incorporation pending) known as the Allied Health Manpower Council of Santa Clara County. The Council is composed of representatives in the health professions (physicians, nurses, LVNs and dentists), administrative branches of four junior colleges, San Jose State College and Stanford University, hospital administrators and nursing home administrators, and two representatives from the racial minority groups. The Council was formed in early 1967 and is occupied with the broad problem of increasing the number of persons being trained and employed in the various health fields in this county. With the ratio of "allied health personnel" having increased from the figures of ten such persons for every one Santa Clara County physician in 1960, to 13 to 1 in 1968, and an expected increase of 17 to 1 in 1973, there appears a statistical potential increase of more than 3,000 new employment opportunities each year, not including required replacements.

The Allied Health Manpower Council has held six meetings per year. It conducts its primary functions through its Executive Committee and its Interview Committee for Military Manpower. The Military Manpower Committee's current function is to interview corpsmen who have been contacted by the Council's paid staff personnel. Committee interview schedules are set up, and present at each is an educator, a physician, a nurse, a representative of the Department of Employment and Lt. Myron Corbett, USN, a former medical corpsman and currently the Medical Administrator at Moffett Field Air Station, Mountain View, California. Lt. Corbett serves as a part-time paid consultant to the Medical Society. (The Society practices what it preaches.)

Of the 73 corpsmen already contacted and interviewed, arrangements have been made for 41 to have either part- or full-time employment in a health situation or full-time enrollment in junior or state college courses leading to employment advancement or eventual licensure, or a combination of these various conditions. A tabulation of the endeavors, enrollment and employment of each person is compiled or revised each month.

Recruiting Medical Corpsmen

The success to date for those who have been contacted rests primarily with Mrs. Margo Savage, director of the State Department of Employment office in San Jose and the valued contacts which have been made by Lt. Corbett in his own (Moffett Field) and other Navy installations located around San Francisco Bay. Lt. Corbett currently has under his command 50 medical corpsmen. He has tabulated the data for the termination of those completing an initial enlistment and those ending a "service career" of 20 or more years. These terminations will total about 24 per year in this installation and Lt. Corbett has little difficulty in personally following the career expectation and future plans of each of his men. Since he has a goal of his own set for a position in the private health field 2 years hence, these activities come quite naturally to him.

There are approximately 65 medical corpsmen at the Alameda Naval Air Station and it is estimated that approximately 30 of them are released per year. The Monterey Naval Station has 30 corpsmen, of whom probably ten per year would be released. Letterman General Hospital in San Francisco has approximately 700 corpsmen, but since most of them are "career men," only about 10 percent, or 70 men, would be released per year.

The U.S. Naval Hospital at Oakland has approximately 700 corpsmen and these are in the same general category as those at Letterman and release of only about 10 percent a year is expected. So far as we know, there is no "Lt. Corbett type" recruiter at the Oakland Hospital or at any of the others. There does exist in Oakland, the I&E office (Information and Education). There, the corpsmen can request such information as is available. But with more than 500 or so different types of education or employment opportunities describable, no special attention is given to any particular field of potential employment. A corpsman who possessed certain craft skills before his enlistment may seek to return to that chosen field when his term of service ends. While he is in the service he can take advantage of the correspondence courses conducted through USAFI of Madison, Wisconsin, and enhance his education with instructions and examination that can help him rise from "high school dropout" to a graduate and then on to completion of college credit courses. In these instances, the man must

seek the information and opportunity on his own initiative, spurred only by infrequent mimeographed memorandums and bulletin board posters. That is not enough to induce him to seek future employment in the health care field in his chosen California community, where he may find himself both state unlicensed and locally unemployable.

At the separation centers, where there might be an opportunity for a more significant contact, the "contact time potential" does not usually exceed 12 hours and his momentary interests are more likely to be his friends, his family, and a warm private bath. His attitude is quite likely to be that his future can wait. Evidence that prior contacts may be more productive, though more difficult to achieve, is contained in the fact that of the 73 contacts we have completed so far, eight involve corpsmen who will be released in 1970, 1971, and 1972. These eight men are very interested in this project; all are seriously exploring suggested sources for additional health career education so that they might attain employment and licensure at as early a date as possible following their release.

As stated in the REMED report, the prime difficulties encountered in corpsmen recruitment are the deterrents to contacting medical corpsmen *before they are released*. It must be realized that these corpsmen are located in almost every military establishment. Contact is extremely difficult and the only new thought and approach to the problem that we have under consideration concerns ways to create contact with the families of corpsmen residing in Santa Clara County. This will be done through the media of newspapers, radio and television appeals. Through such contacts we might be able to determine the approximate discharge date for a number of corpsmen. We would then initiate correspondence and an exchange of information with them through their families and friends.

We believe that the "through-their-families" approach to potential medical corpsmen recruiting should not be attempted in any community unless the following conditions exist: (1) The community's facilities have the capability to provide health care-related study courses that can enhance the corpsman's education to a point where he can qualify for paramedical jobs or become eligible to take a professional licensure examination, and, (2) the community's health services industry and professions have employment opportunities that

are attractive in nature, remunerative, and can be filled by retrained, licensed or unlicensed former medical corpsmen, either male or female. A realistic affirmation of employment opportunity for former corpsmen must be secured from potential employers before "generalized" encouragement is extended to corpsmen through family members in a given community.

Licensure, Certification

Unspecified problems related to licensure and professional liability responsibilities must be resolved jointly by all health professions, their associations and their licensing boards before truly significant strides can be made to greatly expand the total health manpower working force.

The training and medical service experience of corpsmen varies from service to service, but the higher levels of attainment apparently rest with the Navy, the Air Force and the Coast Guard. There is less likelihood of there being great numbers of well qualified corpsmen in the Army since most of the enlistments there are for only 2 years. Most released corpsmen are willing to continue the health related education. Sixty-nine percent of these in the project plan to go on to achieve licensure as an LVN or an RN or to try for an M.D. or a baccalaureate or master's degree. Only 31 percent, so far, are enrolled in Associate Arts Courses.

Recently enacted legislation in California will ease the specific number of months of "military corpsman service" required to qualify for taking either the RN or LVN licensure examination.

At the moment, released corpsmen can take the examination in California for licensure as a psychiatric technician if they take one year of junior college training before the date of the examination. This favorable situation is a temporary one only; it is to expire 1 January 1970. In this contact group, two men are seeking to take this examination, but it is not certain whether they will be able to do so before the expiration date.

Officials of the Allied Health Manpower Council think that the California Medical Association might explore the expansion of such examination privileges for released medical corpsmen in the licensure fields of x-ray technicians, laboratory technicians, inhalation therapists, sanitarians, entomologists and veterinarians. The CMA might also explore, they say, the possible creation of a "certification" status in a variety of fields not cur-

rently covered by licensure requirements and apparently not likely to reach that stage. These include the occupations of orderlies, nurses aides, traction set-up technicians, hospital patient release coordinators, medical claims review specialists, and clinic managers.

Another matter that should be studied, and acted upon if possible, because it is a current deterrent to re-employment and licensure of medical corpsmen, is the time and location of the examinations that are currently being given. For those living in California, some examinations are given only in Berkeley or Sacramento, others only in Los Angeles. More flexible arrangements should be available.

The Great and Mighty Apostrophe

As new health occupations are created, a constantly repeated question concerns whether or not these persons who assist physicians will be "practicing medicine." The answer must continue to be "No." Only a licensed physician can practice medicine. Therefore, the lowly apostrophe may take on a mighty significance in the role of identifying each such "assistant" as an "assistant" to a physician—thus: An orthopedist's assistant, not an orthopedics assistant. If such a concept could be created and maintained, boards of medical examiners might be able to open new channels of services by recognizing that all acts of these new health workers would, for each such act, be under the direct orders and control of a specific individual physician. The one individual physician may change from day to day, or even during a single day (as in the instance of employment in a group practice setting). However, in each instance, the health worker, or "certified assistant" would be a "physician's assistant"—*singular-possessive*.

Conclusions

- For maximum desired results, recruitment of in-service medical corpsmen for employment in civilian health care fields must begin before the corpsman's date of release from service.
- There is not now in force a useful, workable "contact" system to reach corpsmen with civilian health care services education and employment opportunity information before they leave the service.
- The only new approach for pre-release contacts that has been suggested is that of developing contact through local family members of in-service corpsmen.

Abortion in California

State Supreme Court Decision under Former Law Sheds Some Light on Conduct under Amended Act

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THE CALIFORNIA SUPREME COURT'S landmark decision in the case of *People vs. Belous*, involving a conviction under the criminal abortion law as it stood in 1966, has received national attention. *Time* magazine and other publications have reviewed the events which led to Dr. Belous' conviction, and the Supreme Court's action in setting it aside. California physicians are therefore interested in the current status of abortion laws in California.

It is important to understand that the Belous decision dealt with the criminal abortion law as it existed in 1966, before the present Therapeutic Abortion Act was adopted. At that time, Penal Code 274 provided that:

"Every person who provides, supplies, or administers to any woman, or procures any woman to take any medicine, drug, or substance, or uses or employs any instrument or other means whatever, with intent thereby to procure the miscarriage of such woman, unless the same is necessary to preserve her life, is punishable by the imprisonment in the state prison not less than two nor more than five years."

Section 274 was amended when the Therapeutic Abortion Act was adopted. It is now unlawful to "procure the miscarriage of such woman, except as provided in the Therapeutic Abortion Act." In the Belous case, the court did not pass upon the legality of the present statute. While the court provides some clues as to what the law may be, the court has not declared the present state of the law.

In throwing out the old statute and Dr. Belous'

conviction, a majority of the court held that Section 274, before amendment, was unconstitutional because the term "necessary to preserve her life" is so vague and uncertain as to deny due process, stating that men of common intelligence must not be required to guess at the meaning of the phrase.

Two possible definitions of this phrase were discussed in the hearing. It was urged by state's counsel that the law prohibited abortions unless the patient would die without the abortion. In response, the court cited previous California decisions rejecting certainty or immediacy of death as the standard. The court considered an opposing contention, which is that abortion should have been authorized under the old statute whenever there was the mere possibility of death if the patient should bear her child. In the mind of the judges, this interpretation would render the old statute "virtually meaningless." In this connection, the court observed: "Moreover, to determine the right to an abortion solely on the basis of the dangers of childbirth without regard to the relative dangers of the abortion would be contrary to good medical practice."

After rejecting the conflicting definitions of "necessary to preserve," the court suggested a test which it feels would be constitutional. The court observed that the legislature may have intended that abortion was permitted when the risk of death due to abortion would be less than the risk of death as a result of childbirth. It is pointed out that this test would involve an application of medical principles only. The court specifically rejects the contention that abortion statutes are intended to protect the fetus. It may be noted that

this "relative safety test" is analogous to the test now contained in the Therapeutic Abortion Act.

Although the court apparently approves of a "relative safety test," it overturned Dr. Belous' conviction, and declared Section 274 (before amendment) unconstitutional, on the grounds that the persons concerned, particularly physicians, should not have to choose amongst the various conflicting definitions. Three of the seven justices dissented, and would have upheld the old statute.

Since the court was concerned with the law as it was, several questions remain unanswered. It would certainly be erroneous to construe the court's decision as holding that the legislature has no rights to restrict the performance of abortions. It seems clear that the court recognizes that there may be an area in which the legislature can validly exercise its police power, to protect the health of its citizens. On the other hand, it must be noted that the court, in formulating the "relative safety test," seems to imply that this assessment should not involve non-medical considerations.

It is difficult to make any statement as to the present status of the Therapeutic Abortion Act, except to say that the validity of the restrictions contained in that act is in doubt. While even this portion of the opinion is somewhat ambiguous, it does seem that the court feels that a woman has a constitutional right to decide whether she should bear a child. It appears that the court is prepared to hold that the only proper limitation which may be imposed on this right is one which is de-

signed to protect the woman's health. This would be a decision based solely upon medical considerations.

If this interpretation is correct, the court may hold that the provision of the Therapeutic Abortion Act which permits abortion only when "there is substantial risk that continuance of the pregnancy would *gravely impair* the physical or mental health of the mother" is unduly restrictive. The majority decision would seem to permit the state to deny an abortion only when the performance of the abortion would be relatively dangerous, compared with the probable consequences if abortion were not performed.

A petition for rehearing was denied, and the decision is now final. The next chapter will be written if the restrictions set forth in the present Therapeutic Abortion Act are challenged in some new litigation. Attorneys familiar with this controversy believe such litigation is likely. While the status of those provisions restricting the circumstances in which abortion is allowed is unclear, there is no indication that the court will strike down either procedural requirements for committee review or the requirement that abortions be performed in an accredited hospital. Pending further litigation, and judicial interpretation of the present law, hospital committees have generally been advised that they must continue to apply the law as it is now on the books, unless the legislature itself acts to resolve the questions posed by the Belous decision.

ANTACID THERAPY FOR HIATAL HERNIA

"A mainstay of therapy for . . . hiatal hernia is the antacid. . . . It doesn't really matter what antacid one gives; what's important is the way one gives the antacid. In our institution we usually utilize hourly antacids during the waking hours for about two weeks. On the fasting stomach this becomes most important since the antacid will usually leave the stomach about every 40 to 60 minutes and ought to be replaced. After two weeks of therapy, we usually move on to an every two-hour regimen, and for another two to three months we'll administer antacids about one hour after each meal and at bedtime. In most cases, antacid therapy will stop within three months."

—LAWRENCE D. WRUBLE, M.D., Memphis
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University of California

School of Medicine

San Francisco Medical Center

FROM THE VANTAGE POINT of more than 100 years, the University of California School of Medicine, San Francisco, looks toward a future filled with new challenges and exciting potentials. Growing to meet community needs and assuming leadership in the health sciences is part of the school's long tradition rooted in a heritage which dates back to Barbary Coast days. Founded in 1864 by Dr. Hugh Hugher Toland, the School of Medicine in San Francisco was the second medical college in California: It remains, today, the oldest one in the state in continuous service. It is also the oldest of the university's five medical schools; has the largest undergraduate enrollment; and has the most extensive public service program.

During the 15 years following the discovery of gold in California, the quiet little town of San Francisco increased in population from 850 to 112,000. Dr. Hugh Toland was one of those who came west seeking gold in 1852, but his luck failed him in the gold fields. He came down from the mountains, then, to practice medicine in San Francisco, which had grown into a raucous, bustling town where a surgeon's skill was frequently needed. Trained for 2 years in France by some of the best surgeons, Toland had skill that developed for him a busy private practice. As a result of his knowledge of health needs in the camps he also built up a lucrative mail order business, prescribing and supplying pharmaceuticals to the inhabitants of the mining camps.

Dr. Toland realized another need, however, and that was for a medical facility in the West where new physicians could be trained. A successful man, himself, Toland proceeded to use his money, knowledge and influence to assemble the first

faculty of ten physicians to staff the newly founded Toland Medical College. On 5 November 1864, the original class of eight students began instruction. Nine years later, after a series of negotiations conducted mostly by University President Daniel Coit Gilman and by Dr. Beverly Cole, dean of the medical college, Toland's school became the University of California Medical Department. It was through further efforts and planning by Dr. Cole that the Affiliated Colleges were initiated, next, and a site provided for them by a generous gift of land from Adolph Sutro, Mayor of San Francisco.

The three Romanesque buildings erected to house the schools of Medicine, Pharmacy and Veterinary Science and Law were completed in 1898. All now have disappeared under the wrecking-ball to make way for taller buildings. Houses now cover the sand dunes that surrounded the old campus, and the forest on the north slope of Sutro Forest has been thinned to accommodate student housing, auxiliary buildings, and parking lots. The schools of Law and of Veterinary Science had only a brief sojourn on Parnassus Heights, but the schools of Medicine and Pharmacy, joined later by Dentistry and Nursing, remained to expand in response to the needs of a rapidly growing California population.

Educational Programs

During the past 105 years, the School of Medicine's enrollment has increased from eight students to the 522 who now are working toward a doctor of medicine degree, 97 interns accepted under the National Intern Matching Program, 445 residents enrolled in 16 different specialty programs, 178 post-doctoral fellows training in 18 specialized areas and 114 candidates working for advanced

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degrees in disciplines that include anatomy, biochemistry, biophysics, and endocrinology, comparative pharmacology and toxicology, microbiology, and public health. These students study and conduct research in departments of the School of Medicine.

The school is also cooperating in a community effort to expedite training programs in allied health areas directed toward relieving the health manpower shortage. Laboratory and hospital facilities are necessary for the clinical training required to supplement instructional programs which are primarily the responsibility of junior and state colleges. Critical space limitations preclude a major increase of these students at UC, but programs will be developed to train a substantial number of Allied Health Professional students in affiliated institutions, the main thrust being to provide a source of instructors.

Social legislation, increased population, developing technology, and demands for better quality medical care have intensified the health manpower shortage throughout the country. Although 85 percent of those receiving degrees in medicine from schools in California remain in the state, California still must rely on out-of-state graduates to meet its needs. By 1979, the number of new physicians needed in California, alone, will be 2,099 annually; local schools will provide only 26.3 percent of this vital manpower requirement. The remainder, as it does today, will have to come from out-of-state sources.

As part of the effort to meet this crisis in health manpower, the School of Medicine is expanding its training programs and has introduced a new curriculum this fall. During the past 4 years, enrollment of freshmen working toward an M.D. degree has been increased from 100 to 134 students. A total increase of 84 students by 1980 is anticipated.

Curriculum Changes

In 1966 the school adopted a revised traditional curriculum, accommodated within the 4-year lock-step program. Included in the revision were the addition of major interdisciplinary courses in basic sciences and clinical fields, expansion of the elective period to a full quarter, and increased clinical responsibility for senior students. The Division of Ambulatory and Community Medicine was established, also, which provided new areas of teaching

and community involvement with emphasis on comprehensive health care.

The other professional schools on campus — Dentistry, Nursing, and Pharmacy—were incorporated into this interdepartmental and interschool instruction-research unit. Lack of space and funds prohibits more rapid expansion of training capacity and, as on other UC campuses, building programs have been greatly curtailed during the past 2 years because of funding cuts.

The new curriculum, which was approved 23 July 1969 by the faculty of the School of Medicine, is a major effort to meet current and future health needs by more imaginative and efficient approaches to teaching in medicine, by consolidation of faculty-student efforts, and by fuller utilization of existing facilities. It was launched with the enthusiastic support of faculty and students and is now in effect. The degree to which students were involved in planning the new curriculum is one of its most unique features. The contributions made by them as members of the planning committee were invaluable. Active student participation at the policy, planning, and operational levels of academic affairs is considered essential by the faculty and administration of the School of Medicine, and is encouraged.

Because no curriculum is ever perfect, a curriculum should, ideally, be a process of continuing evolution. It is hoped that the newly approved curriculum, with its emphasis on flexibility, will allow the transitions necessary to accommodate growth and changing demands during the coming years. The former linear curriculum with its rigid, 4-year progression has been exchanged for a program designed to have greater relevance to present and future health needs and to take advantage of the student's ability and interests. The health science student of today is intellectually well-prepared, is concerned about social conditions that effect health and the delivery of health care, and has a strong commitment to service.

Following the concept of a college major, the new program is structured around a required core-curriculum which occupies approximately 70 percent of the student's time, with the remaining 30 percent open to electives. Within this framework a student may choose one of six major pathways: Medical Specialist, Medical Scientist, Family Physician, Behavioral Specialist, Surgical Specialist, and Social Administrative Medicine. This system of pathways provides an opportunity for study in

depth without forcing the student into premature specialization. The flexibility which is provided within this framework should develop better understanding of a field and the methods used in it, as well as a better understanding of the application of scientific method in medicine.

It is anticipated that most students will choose patient-oriented courses early in their studies, and this introduction of clinical instruction during the first 2 years is expected to increase the value of basic science courses which may now be taken at a much later time than was possible under the old traditional curriculum.

Major advantages, then, of the new curriculum are: year-round operation; admission to advanced standing in all four quarters; flexibility in course sequence; flexibility in the amount of time for completion, with a minimum of 3 years and a maximum of 5 years; major programs for all students; and increased elective time for all students.

Built into the new program are a comprehensive orientation program, and an advisory-counseling system that utilizes both faculty and students. The advisory system revolves around 10 or 11 groups, each composed of four faculty members and three students. Entering students will be assigned at random to these groups. It is intended that this advisory-group system will provide greater accessibility to the faculty for students and subsequently more comprehensive counseling and closer working relationships.

Coordinated within the school's new curriculum, a Medical Scientist training program was initiated this fall for those interested in academic careers. A reliable source of competent faculty is of prime importance to sustain the training of physicians of high quality. In 1967 it was estimated that, nationwide, there was a shortage of approximately 50,000 physicians; and an even more critical shortage is projected to occur during the next 10 years. This affects not only the practicing physician but the full-time teaching physician as well. A lack of programs especially designed to prepare physicians for faculty careers, as well as direct drains on this manpower group, contribute to a shortage of medical faculty today. A considerable drain of medical faculty has already occurred because of the rapid expansion of medical schools and development of new ones, and new large-scale federal health programs also have absorbed faculty members.

Under the Medical Scientist program provision is made to accept six trainees now in this program which is designed to fulfill the requirements for both the M.D. and Ph.D. degrees, and a total of 12 will be enrolled by 1972. Depending upon the area of emphasis in training, graduates of the program will enter directly into a teaching career in clinical medicine or in a basic science department. The first 3 years, trainees will enroll in all courses required for the M.D. degree; the fourth year they enter a basic science department of their own choosing; and the remaining 2 or 3 years of the program is dictated by the choice of clinical medicine or basic sciences.

This training program structured to prepare clinical and basic science teachers in medicine allows the student to differentiate courses earlier, coordinate clinical and basic science information more efficiently, and reduces the total period of education. A stipend support to the students has been requested from the USPHS.

Student Participation

Development of the new curriculum is only one of many areas of academic importance where students in the School of Medicine take part in planning and decisions. The students' involvement in academic affairs is deemed to be vital to the growth and progress of the school. About 2 years ago, the Student Welfare Committee was formed. It is composed of eight students and seven faculty members. This committee directs its efforts toward improvement of conditions for students at both the academic and personal level and has been helpful in placing students on other committees.

It is evident that students are more cognizant of their immediate problems than are faculty members and, as full voting participants, can provide direction that is relevant to their specific needs. We have found that this approach not only increases the rapport between faculty and students but it also increases the students' sense of responsibility, being active in making decisions, they must also share in the resulting failures as well as in the success. The students working on committees become resources for their classmates, who then feel they have direct representation. This lessens the distance between faculty and students and establishes increased trust. The young student and the older faculty member become more aware that each has something special to offer the other

and that together they can join in a constructive effort.

The recruitment of minority students is one of the outstanding examples of effectiveness which students can achieve in a close faculty-student effort. Defining the minority student as "... those who are socio-economically different from the majority of persons and who because of socio-economic difference would, without special assistance be unable to pursue a course of higher education or would be able to do so only with disproportionately greater difficulty," ... the School of Medicine will admit 32 minority students this fall.

The recruitment program was started in 1966 on the recommendation of the faculty and was supported by funds from the chancellor. That year a black faculty member visited 34 southern colleges to provide information to faculty advisors and students about educational opportunities here in the School of Medicine. During the next 2 years, recruitment was limited to schools in California and in 1968-69 both black and white students became involved in recruiting. They visited each of the 120 college campuses in California, devoting most of their weekends to the goal of having a sufficient number of applicants to fill 25 percent of the freshman class for the fall of 1969. This combined effort by faculty and students resulted in a five-fold increase in applicants, 32 of whom have been accepted for enrollment.

This highly successful recruitment program makes the school a national leader, with the largest number of minority enrollees for this fall of any medical school in the country except Meharry and Howard.

Other committees of which students are members or serve as chairmen are: Advisory Board of the School of Medicine; Committee on Admissions; Committee on Hospital and Clinic Operations; Committee on Scholarships and Awards; Committee on Student Research; and the Subcommittee on Curriculum which is divided into committees concerned with Content, Course Definition, Course Planning, Structure and Mechanisms, Major Pathways, Student Advisor and Orientation Program, Clinical Clerkships, and the steering committees.

Last January, the San Francisco Medical Society invited student representatives to join with them in discussing a proposal to include students on the society's committees. Since May, students

have been members of the San Francisco Society's committees on Legislation, Aging, and Chronic Illness. It is expected that additional students will join other committees during the coming year.

Community Affiliations

Although the principal nucleus of training facilities for medical students, interns, residents, post-doctoral fellows and those working for advanced degrees is the San Francisco campus, co-operative agreements extend clinical and research training programs into other Bay Area institutions. In the immediate area, these include San Francisco General Hospital, Laguna Honda Hospital, Veterans Administration Hospital, Childrens Hospital and Adult Medical Center, Franklin Hospital, Pacific Medical Center, Shriner's Hospital for Crippled Children, Harkness Pavilion, and the USPHS.

Others in the adjoining Bay Area include: East Bay Childrens Hospital and Highland General Hospital, Oakland; East Bay State Mental Hygiene Clinic and Cowell Memorial Hospital, Berkeley; Mills Memorial Hospital, San Mateo; Kaiser Rehabilitation Center, Vallejo; Fairmont Hospital, San Leandro; Sacramento County Hospital, Sacramento; Santa Clara Valley Medical Center, San Jose; and Sonoma State Hospital, Eldridge.

Under contract to the City and County of San Francisco all clinical services at San Francisco General Hospital are provided by faculty who have clinical or full-time appointments in the School of Medicine, and an associate dean is assigned to plan, coordinate and develop programs that facilitate teaching and research. A two-way closed-circuit television operates between there and the campus on Parnassus, which permits classroom lectures, seminars, and grand rounds to be shared simultaneously. San Francisco General Hospital is a city-owned and city-operated 916-bed institution. During the past several years under the impetus and supervision of the School of Medicine a coronary care unit, intensive care unit, kidney dialysis center, and general clinical research center have been established there.

A 783-bed hospital to replace the present structure is planned for completion by 1974 on property adjoining San Francisco General Hospital. This complex, funded by a city and county bond issue, will be available as a city-wide referral center for special problems such as those of alcoholism, geriatrics, childhood and adolescent psychiatry, renal dialysis, pulmonary diseases, infectious dis-

eases, and trauma, and also for emergency services. Mental hygiene and psychiatric facilities will be decentralized in five district centers.

Hospital facilities on the UC campus have been in need of expansion for some time and with increased enrollment in the School of Medicine, as well as in other schools, the need will become even more acute. A 206-bed addition to Moffitt Hospital with increased laboratory and other training facilities has been projected but not funded. The clinics, long overcrowded, will be moved into a new building now under construction which is scheduled for occupancy in 1971. The structure—located on the north side of Parnassus—will be nine stories high, with the lower five levels terraced down to Irving Street for a parking garage.

During the year 1967-68 there was a total of 16,275 patient admissions in the Herbert C. Moffitt and UC Hospitals on campus. For the same period there was a total of 19,967 admissions at San Francisco General Hospital. Outpatient visits at UC's clinics totaled 255,000, and at San Francisco General Hospital 155,428.

A new, major affiliation was initiated in 1968 between the School of Medicine and Veterans Administration Hospital at Fort Miley, with the objective of developing broader patient-care, teaching, and research programs of high quality. An associate dean of the School of Medicine serves as chief-of-staff at this hospital and he is responsible for program development and supervision. This is considered a campus-wide affiliation and, therefore, includes the deans of the schools of Nursing, Dentistry, and Pharmacy as members of the policy-making body. The Dean's Committee of the School of Medicine strongly supports the development of patient-care and research by these schools at Veterans Administration Hospital in coordination with the campus medical programs. Under this new affiliation, medical student and resident education programs have been established which are integrated with those at UC.

The Veterans Administration Hospital is a 352-bed institution which serves as a referral center for veterans and retired federal employees from Northern California. A new 470-bed hospital, scheduled for completion by 1974, will replace the present structure.

Regional Medical Programs

The School of Medicine, as part of the University of California San Francisco Medical Center,

through its more than 50 specialty clinics has served for many years as a consultation and reference source for Northern California physicians. This steadily growing involvement with surrounding communities was expanded recently through the school's affiliation with the nationwide, federally sponsored Regional Medical Programs (RMP). In its function of increasing the quality of health care and its delivery, and of providing a new kind of post-graduate training for physicians, Regional Medical Programs involves the School of Medicine with many community hospitals and health agencies in what is designated as Area I in California. This consists of the Bay Area counties and those in northwestern California to the Oregon border. Each community within Area I is a potential nucleus for in-depth continuing education which will assure its people of high quality medical care. In a service capacity, under RMP, the School of Medicine extends its teaching and training resources to these communities at their request. The decentralized structure of the training programs enables them to reach physicians and other health personnel in their own communities. These programs are an effort to increase the effectiveness of existing health manpower. Through this community-university effort, seven major projects have been initiated under RMP since the initial planning grant awarded in April 1967. Five new proposals are under review. Those already in progress are: A Confederation of Coronary Care Units, Training in Intensive Care Skills for Physicians in Small General Hospitals, Regional Hypertension Program, Rehabilitation and Continuity of Nursing Care Services, University Medical Center-Rural Community Hospital Cooperative Demonstration Program, Regional Cancer Program-Phase I, Intensive Care in Cardiopulmonary Resuscitation for Emergency Rescue Personnel, and an Administrative Core Planning Grant.

Other RMP programs projected for the future include those oriented to problems of poverty areas. Medical needs of the black community were the subject of a symposium funded last spring by RMP and sponsored by the John Hale Medical Society. Community leaders, the Hunters Point-Bayview Community Health Center, and other service organizations are at present involved in exploring ways to improve both the availability and quality of health care for the disadvantaged.

STUART C. CULLEN, M.D., Dean

Information

Prosthetic Replacement of the Mitral Valve: An Assessment of The Clinical and Hemodynamic Results of Operation

ANDREW G. MORROW, M.D.

Material Supplied by the California Heart Association

THE STARR-EDWARDS prosthetic mitral valve has provided surgeons with a means for correcting malformations of the mitral valve that are not otherwise amenable to operative treatment. These malformations may be generally classified as rheumatic mitral regurgitation and calcific mitral stenosis, although, rarely, valve replacement is required in a patient with congenital heart disease. In many other patients with pure or predominant mitral stenosis, the valve may retain reasonable mobility and remain free or nearly free of calcification. In such patients, who are usually young women in regular sinus rhythm, relief of obstruction can be achieved by digital or instrumental mitral commissurotomy, and this safe and simple closed operation should be applied whenever possible. In contrast, when a stenotic valve and the supporting subvalvular structures are heavily calcified and densely fibrotic, effective function can almost never be restored, even by debridement and commissurotomy under direct vision. In this clinic the results of reconstructive operations for mitral regurgitation have also been poor; moderate to severe regurgitation has recurred in virtually all patients after one to two years, even though the valve was competent in the early postoperative period.

The Starr-Edwards prosthetic valve has been used at the National Heart Institute since 1961, and has been inserted in more than 300 patients.

Dr. Morrow is Chief, Clinic of Surgery, National Heart Institute, Bethesda, Maryland.

Recently, the early and late results of operative treatment in 100 consecutive patients were reviewed, and these are summarized in the present report.

The Patients

The 100 patients all had acquired mitral valve disease, and two-thirds gave a clear history of previous rheumatic fever. Fifty-three were female, 47 were male, and they ranged in age from 10 to 64 years; the mean age at operation was 38 years. All patients were distinctly symptomatic, and 34 were in Class IV (NYHA), 64 in Class III, and two in Class II. Admission to hospital for the treatment of congestive heart failure had been necessary on one or more occasions in 87 patients, and 38 had been in hospital three or more times. Previous operations on the mitral valve had been performed in 35 patients.

The characteristic clinical, radiographic, and electrocardiographic findings of mitral stenosis, mitral regurgitation or a combined mitral valvular malformation were evident in each patient. In 36 patients signs of tricuspid regurgitation were also present, and 24 patients had physical evidence of aortic regurgitation, but of insufficient severity to necessitate aortic valve replacement. Calcification of the mitral valve was evident fluoroscopically in 63 patients.

All of the patients were studied by right and 95 by left heart catheterization preoperatively. On the basis of the preoperative hemodynamic and angiographic assessments and the operative findings, 50 patients were considered to have pure or predominant mitral stenosis, and 50 to have pure or predominant mitral regurgitation. In the entire group of 100, severe pulmonary hypertension (systolic 50 mm of mercury or more) was present in 69 patients, and the average cardiac index was reduced to 2.1 liters per minute per square meter. Preoperatively, the left atrial mean pressure was abnormally elevated in 96 patients (average 22 mm of mercury); a diastolic gradient across the valve was recorded in all patients with mitral stenosis and in 33 of those with mitral regurgitation.

The Operation

In most patients the operation was performed through a left lateral thoracotomy (with right ventricular cannulation for venous return), and in the remainder a median sternotomy or right thoracot-

omy was employed. Cardiopulmonary by-pass was usually conducted at 37° C, but mild (30° C) general hypothermia was induced when aortic regurgitation necessitated numerous or prolonged periods of aortic occlusion. Ventricular fibrillation was induced in most patients by AC stimulation.

When the necessity of valve replacement had been determined, the valve was excised in continuity with the chordae tendineae and papillary muscles. Residual calcific deposits in the annulus were removed with a rongeur, and the ventricle was lavaged. The prosthetic valves employed were those supplied by the Edwards Laboratories at the time, and all had bare metal orifices and struts and silastic poppets. Size 3M or 4M valves were inserted in 90 patients, while nine received 2M valves, and one a 5M. The valves were anchored by 15 to 20 interrupted sutures, each passed twice through the fixation ring of the prosthetic device and the patient's valve ring. In 17 patients a left atrial thrombus was present, and was excised before valve replacement; in six of these cases, calcification of the left atrial wall was evident preoperatively.

In the immediate postoperative period, assisted ventilation was provided via the endotracheal tube for 12 to 24 hours, and in 34 patients longer periods of assistance necessitated tracheostomy. Anticoagulation with warfarin was instituted 48 to 72 hours after operation.

The Results

Immediate Mortality: Seventeen of the 100 patients died during the hospital admission at which valve replacement was carried out. Two patients died in the operating room; one had uncontrolled bleeding from the atrium, and in the other effective cardiac contractions could not be restored after by-pass. Eight patients died one to seven days after operation with progressive hypotension and signs of reduced cardiac output; all had normal or small left ventricular cavities. At necropsy it appeared that obstruction to left atrial outflow had been produced by incomplete descent of the prosthetic ball that, in turn, resulted from protrusion of the muscular ventricular septum into the cage. In five of the eight patients massive thrombosis of the valve and atrium had occurred. Two other patients died of acute myocardial infarction, one the result of a coronary arterial embolus. One patient died of cerebral embolism from air trapped

in the atrial appendage, and another from infected pulmonary emboli which had been present preoperatively. The remaining three patients, all young women with mitral regurgitation, died one or two days postoperatively after evidencing cardiac failure and hypotension; no anatomic cause of death was evident at necropsy.

Late Mortality: Seven of the 83 patients who survived the immediate postoperative period have died, five months to two years later. Two had infectious endocarditis; in one patient the infection followed an intercurrent operation performed without the administration of antibiotics. One patient had a fatal cerebral embolus after her physician had discontinued warfarin administration for unknown reasons. Another patient had a subarachnoid hemorrhage as a result of warfarin overdosage. One patient died in heart failure after an unsuccessful attempt to close a peribasilar fistula. In the remaining two patients death was sudden and unexpected and the cause is unknown.

Thromboembolism and Anticoagulation: An attempt has been made to maintain all patients on therapeutic doses of warfarin, but this aspect of the patient's management has been under the control of the referring physicians. Nine patients have had definite cerebral emboli, and in two of these cerebral embolism occurred on two different occasions. As noted above, one of the patients with cerebral embolism, who was not receiving warfarin, died. Another has persistent flaccid hemiparesis and is severely incapacitated. Two patients have neurologic abnormalities on examination, but they are asymptomatic. The other five patients who had cerebral emboli have no detectable abnormal findings. Five additional patients have described transient vertigo, amnesia or muscular weakness, but in them no neurologic abnormalities have ever been detected on any examination.

One patient died as the result of warfarin toxicity, and two others have had massive but non-fatal episodes of gastrointestinal bleeding.

Clinical Status: The 76 surviving patients have been followed for intervals of two to six years. Forty-seven of them are asymptomatic (Class I), 26 are in functional Class II, and three are in Class III. Preoperatively, 52 of these 76 patients were in Class III and 23 were in Class IV. Fifty-three patients are working full-time or, in the case of some women, managing their homes and families without unusual assistance. Sixty-nine patients are on unrestricted diets.

Postoperative Hemodynamic Assessments: The resting pulmonary arterial pressure was lower postoperatively in every patient in whom it was abnormally elevated before operation, and the systolic pressure was less than 50 mm of mercury in 71 of 74 patients studied. The left atrial mean pressure was also reduced in every patient in whom it had been abnormal, but in 15 of 68 patients it still exceeded 12 mm of mercury. The cardiac index was higher postoperatively in 63 of 67 patients, and the average postoperative value was normal, 2.9 liters per minute per square meter.

Some Conclusions

The experience with mitral valve replacement in these and other patients allows certain conclusions concerning the present status of the operation, and permits some predictions as to its future applicability. The immediate operative risk continues to approximate 10 percent, and will probably not become significantly lower as long as the operation is reserved for severely ill patients, those in Classes III and IV. The Starr-Edwards prosthetic valve is the subject of constant reevaluation

and improvement, and as the long-term reliability of the valve improves, operation reasonably can and should be recommended to patients earlier in the course of their disease. The incidence of death and disabling complications in the late postoperative period has thus far been distinctly lower than in patients with prosthetic aortic valves. Arterial emboli have occurred in about one-fifth of patients, in spite of attempt to maintain effective anticoagulation with warfarin, but significant sequelae of the emboli have been absent or inconsequential except in two patients. Improved prosthetic valves can be expected to eliminate or greatly reduce the incidence of thromboembolism. Of greatest importance is the fact that surviving patients have experienced striking and sometimes dramatic symptomatic improvement, and almost all have been able to return to useful and productive lives and to carry on their increased activities without significant discomfort. The postoperative hemodynamic studies have shown that symptomatic improvement is paralleled by a return of the cardiac output and intracardiac pressures to normal or near-normal levels.

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Survey on Medical Student Attitudes

A Socio-Economic Report of the Bureau of Research and Planning,
California Medical Association

■ *One of the concerns of the Committee on the Role of Medicine in Society of the California Medical Association is the apparent "attitude gap" between medical students and physicians already established in practice. In November 1967, the first of a series of meetings took place between Committee members and senior students from each California medical school. Discussion ranged from curriculum planning to individual and organizational politics, and revealed differences of opinion between students and physicians on such issues as Medicare and the financing of health care for the nation.*

These discussions suggested to members of the Committee that several clearly defined subject areas were worthy of further investigation. It was decided, therefore, that a questionnaire be sent to medical students and residents, with the goal of gaining a better understanding of the nature and extent of such differences of opinion. Some of the highlights of the findings of this survey are discussed in this Socio-Economic Report.

IN NOVEMBER 1968, a questionnaire, designed to elicit information about the areas of concern outlined during the Committee meetings with medical students, was mailed to a random sample of one-third of all first and fourth year students in California medical schools, and to one-third of all those who graduated in 1965, whether now in residency or in practice. In three years, when the current class of freshmen has become seniors, and the seniors residents, the study will be repeated, with a new freshman group, but otherwise using the same samples. At that time, a longitudinal comparison can be made, comparing the same groups over a period of time, to see how attitudes change *within* groups. At the present time, however, only comparisons *between* groups are possible.

In conducting this study, the Committee on the Role of Medicine in Society was primarily interested in gathering two types of information: (1)

What are the differences in attitude among the three study groups on various issues pertaining to American medical care and its future? (2) Aside from these differences between groups, how do the respondents feel about the issues themselves?

I. Responses to the following 11 statements showed no statistically significant differences in attitude between any groups; opinions of freshmen, seniors, and residents are in general agreement.

Statement 5: The struggle against socialized medicine in the United States should now be channeled into other activities, such as cooperation with government, to form a meaningful partnership for the betterment of the health of the American people.

Results: Over three-quarters of each group agreed with this statement.

Statement 6: Continuing advances in science and technology point to the probability that the physician of the future will become more

Reprint requests to: CMA Bureau of Research and Planning, 693 Sutter Street, San Francisco 94102.

of a technician and less of a personal physician.

Results: Responses split fairly evenly between "agree" and "disagree"; a slight majority of freshmen agreed, while a slight majority of seniors and residents disagreed.

Statement 9: In view of the fact that scientific advances progress faster than they can be applied, and of the fact that specialties and subspecialties are proliferating rapidly, it is necessary that medical education be directed toward insuring that the role of the physician remains a very personal, rather than a technical one.

Results: Over three-quarters of each group agreed.

Statement 10: The medical profession must realize that, in the future of American medicine, the health care team is becoming increasingly important with many of the responsibilities of today's physician devolving on auxiliary personnel.

Results: Over 90 percent of each group agreed.

Statement 11: In order to reflect current changes in the social structure, emphasis in medical education must be placed on community and environmental health problems.

Results: Over two-thirds of each group agreed.

Statement 13: Since it is obviously impossible for any one person to learn everything about medicine today, the medical curriculum should be narrowed toward specialization at an earlier stage; for example, the student intending to specialize in psychiatry should not need to study surgery.

Results: Thirty-nine percent of freshmen, 42 percent of seniors, and 35 percent of residents agreed with the statement.

Statement 16: As part of the medical curriculum, a program should be established so that the medical student might learn about the practical side of his profession by working with an established physician.

Results: Over 85 percent of each group agreed.

Statement 19: The response of organized medicine to various governmental programs for the financing and provision of medical care generally reflects the opinions and atti-

tudes of the majority of practicing physicians.

Results: A majority of each group agreed; 41 percent of freshmen did not respond.

Statement 24(A): The medical profession is successfully meeting its professional obligations in the area of: Peer review.

Results: Sixteen percent of freshmen, 25 percent of seniors, and 32 percent of residents agreed with the statement. Approximately one-quarter of seniors and residents, and almost 60 percent of freshmen, did not respond.

Statement 24(C): The medical profession is successfully meeting its professional obligations in the area of: Disciplinary measures against errant physicians.

Results: A minority of each group, including 18 percent of freshmen, 26 percent of seniors, and 35 percent of residents, agreed with the statement; 54 percent of freshmen, 26 percent of seniors, and 14 percent of residents were indifferent or did not respond.

Statement 24(D): The medical profession is successfully meeting its professional obligations in the area of: Experiments in the organization and delivery of medical care.

Results: Only 16 percent of freshmen, 19 percent of seniors, and 23 percent of residents agreed with the statement; approximately one-half of freshmen and one-quarter of seniors and residents did not respond.

II. The following nine statements show statistically significant differences in attitude between students (freshmen and seniors) on one hand, and residents on the other:

Statement 1: The government should have no voice in determining how physicians practice medicine.

Results: Approximately one-quarter of the freshmen, one-third of the seniors, and one-half of the residents agreed with the statement.

Statement 3: In order to maintain its independence, the best course for organized medicine at every level, including the AMA, would be to continue its fight against any effort to socialize medicine.

Results: Twenty-eight percent of freshmen, 28 percent of seniors, and 55 percent of residents agreed with this statement.

Statement 7: Decisions regarding the organi-

zation and delivery of medical care should be entirely in the hands of the medical profession.

Results: Thirty-eight percent of freshmen, 45 percent of seniors, and 54 percent of residents agreed with this statement.

Statement 12: In order to reflect current technical advances, emphasis in medical education must be toward further specialization and sub-specialization, with community and environmental aspects of health care covered by public health functions.

Results: Only 27 percent of freshmen and 31 percent of seniors, but fully 48 percent of residents agreed.

Statement 15: If local medical societies were to offer affiliate membership to medical students at nominal cost, and encourage students to engage in society activities, both organized medicine and the student would benefit greatly.

Results: A majority of each group agreed; one-third of freshmen, one-quarter of seniors, and 15 percent of residents had no opinion.

Statement 21: The concept of periodic relicensing of physicians should not be supported by the medical profession.

Results: Fifteen percent of freshmen, 10 percent of seniors, and 34 percent of residents agreed with the statement.

Statement 23: Hospitals should serve as community health centers, responsible for making available comprehensive health care to the public.

Results: Over two-thirds of each group agreed, with a greater proportion of freshmen and seniors than of residents agreeing.

Statement 24(B): The medical profession is successfully meeting its professional obligations in the area of: Utilization review.

Results: A majority of freshmen and seniors with an opinion disagreed, while a majority of residents agreed. Seventy-three percent of freshmen, 40 percent of seniors, and 37 percent of residents had no opinion.

Statement 24(F): The medical profession is successfully meeting its professional obligations in the area of: Comprehensive health planning for personal and environmental health care.

Results: Eleven percent of freshmen and seniors, and 31 percent of residents agreed with the statement; approximately one-half of freshmen, one-third of seniors, and one-quarter of residents had no opinion.

III. The following three statements show statistically significant differences in attitude between freshmen on one hand and seniors and residents on the other; that is, seniors and residents are quite close in their attitudes, as opposed to freshmen.

Statement 2: Medical care for every individual is a right, not a privilege.

Results: Over two-thirds of each group agreed, with a greater proportion of freshmen and seniors than of residents agreeing.

Statement 4: Quality of medical care is a professional responsibility; government has no role in establishing standards or criteria to assess the quality of care provided to patients by physicians.

Results: One-quarter of the freshmen, 40 percent of the seniors, and almost one-half of residents agreed with the statement.

Statement 20: In order to alleviate health manpower shortages in certain areas, the medical profession should direct the location of physicians to such areas, thereby establishing "ceilings" where an oversupply is deemed to exist.

Results: Approximately one-third of the freshmen, one-quarter of the seniors, and only 16 percent of the residents agreed.

IV. The following three statements show statistically significant differences between freshmen and residents only, with no significant differences between freshmen and seniors, or seniors and residents, indicating a spread of opinion, with no clear-cut "gap" between any two adjacent groups.

Statement 8: It seems only reasonable that government should have a strong voice in determining the organized form of medical practice through which professional services are provided.

Results: A minority in each group, including 29 percent of freshmen, 24 percent of seniors, and 17 percent of residents agreed.

Statement 22: Medical schools should assume the central role not only in the education of physicians, but in determining the nature and

quality of health care services provided to the community.

Results: A majority of each group agreed with the statement, including 64 percent of freshmen and 61 percent of seniors, but only 51 percent of residents.

Statement 24(E): The medical profession is successfully meeting its professional obligations in the area of: Programs of continuing medical education.

Results: A majority of those with an opinion in each group agreed with the statement; 47 percent of freshmen, 20 percent of seniors, and only 7 percent of residents did not respond.

V. The following two statements show statistically significant differences in attitude among all three groups; that is, between freshmen and seniors, between seniors and residents, and between freshmen and residents.

Statement 14: Since medical education is among the longest and most difficult courses of study, and since most graduate students in other fields receive monetary support, the government or some other agency should make nonrefundable support more generally available to medical students.

Results: Eighty-seven percent of freshmen, 80 percent of seniors, and only 66 percent of residents agreed with the statement.

Statement 18: The emphasis of the organized medical profession on fee-for-service solo practice is unrealistic in terms of costs of medical care to the public.

Results: Forty-five percent of freshmen, 39 percent of seniors, and only 27 percent of residents agreed with the statement; 39 percent of freshmen, and approximately one-quarter of seniors and residents, were indifferent or did not respond.

VI. The following statement was unique in showing statistically significant differences between freshmen and seniors, and between seniors and residents, but not between freshmen and residents, indicating that freshmen and residents were in closer agreement than any other two groups.

Statement 17: Solo practice offers greater opportunities for the physician to provide good quality medical care than does group practice.

Results: A very small minority of each group, including 6 percent of freshmen, 2 percent of seniors, and 11 percent of residents, agreed with this statement, while one-quarter of the freshmen, 11 percent of seniors, and 10 percent of residents did not respond.

The following table shows that, while 84 and 85 percent of freshmen and seniors respectively returned the questionnaire, only 68 percent of the residents did so. It seems likely that the extraordinarily high response rate among the first two groups is due to their great interest in the subject matter, although conclusions of this nature must necessarily be tentative. This is undoubtedly the first time that organized medicine has made an attempt on such a scale to solicit the opinions of students. They, in turn, seem to have responded enthusiastically to this opportunity. Since the proportion of residents who returned the questionnaire is significantly less than that of the other two groups, it can be assumed that their attitude toward the entire survey was different—that they found it less interesting, less important, or simply too time-consuming.

*Number and Percent of Returns Tabulated,
by Year of Graduation*

	<i>Total Mailed</i>	<i>Returns</i>	<i>Percent</i>
Class of 1972 (Freshmen)	221	185	83.7
Class of 1969 (Seniors)	162	137	84.6
Class of 1965 (Residents)	136	92	67.7
Total	519	414	79.8

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

The Challenge Ahead

WITH THE PASSING OF THE 1960s, it is appropriate to review public health accomplishments in California during the last decade and to look ahead at problems requiring solution in the next.

Prevention and control efforts have brought considerable progress in communicable disease. For these advances the medical profession and state and local health agencies are responsible.

Constant surveillance has kept up defenses against smallpox, malaria and encephalitis, among other diseases. Poliomyelitis has been virtually wiped out. Measles has declined dramatically. As a result of the priority given to syphilis control and the mobilization of personnel and resources in federally-funded projects in 53 counties, syphilis tapered off steadily beginning about 1964.

In other areas of disease, too, the partnership of medicine and public health has brought gratifying results. Physicians have been responsible for a continuing decline in deaths from cancer of the cervix through widespread application of the "Pap" smear and early detection.

The State Health Department's California Tumor Registry, oldest and largest in the nation, continues to provide essential data for evaluation of various cancer treatment programs, with its record of 300,000 cancer cases dating back to 1942.

The State Health Department, often at the behest of the Legislature, has begun to provide new services and programs based on medical advances and techniques developed during the decade. State funds established two renal dialysis centers, with the Department receiving legislative responsibility for implementing the program. Children with phenylketonuria receive treatment under the Crippled Children Services. The recent development of an

immune globulin to prevent sensitization of newborns in erythroblastosis fetalis resulted in a legislative requirement for Rh-typing of mothers and reporting of sensitized infants to the Department for follow-up.

During the decade the Department has been able to provide new services to California communities:

- In 1964 the Legislature passed a resolution that family planning counseling be made available in public health programs to those who seek it voluntarily.

- In the last half of the decade the Department has offered community-wide services for the mentally retarded through regional centers. Four of the nine authorized centers are already in operation and five more are tooling up.

- A major advance during the last decade is the isolation of the rubella virus. Much of the developmental work in diagnostic tests was done in the Department's Virus Laboratory. With vaccine available, rubella diagnostic tests assume added importance.

- The Virus Laboratory is taking advantage of new developments to meet the challenge of hepatitis, mobilizing personnel to do clinical and field studies and instituting tests to learn the cause, dissemination and pathologic features of hepatitis.

- A major effort of the Virus Laboratory in the next decade will go into determining the possible role of viruses in human cancer. For 7 or 8 years work has been done on animals, but this investigation must be carried over to man.

- A step forward during the decade is the advent of comprehensive health planning. California's medical and public health professionals, together with community representatives, are engaged in statewide planning in many areas of health facilities, services and resources.

On the other side of the ledger, there are many areas which require strenuous efforts in the years to come:

- Efforts to control chronic disease have been less successful than in the case of communicable disease. Little control has been achieved over degenerative diseases, including heart disease and

stroke, and hypertension associated with those causes of death which kill people at a later age.

- Nationwide, the average length of life has increased only a little from 1960 to 1966 — from 69.7 to 70.1 years. We do not know how much life expectancy could be increased if certain factors of disease could be controlled.

- California's infant mortality rate should be lowered. Although it declined from 23.3 per 1,000 live births in 1960 to 19.0 in 1968 and is lower than that of the nation, other states have a better record. Major factors are the existence of high risk populations and the unevenness in availability and quality of medical care services for these groups.

- In 1968 gonorrhea increased for the ninth consecutive year, with 29,000 more cases reported than in 1966. This is partly because of diversion of forces against syphilis at the expense of gonorrhea, but also because of lack of follow-up on gonorrhea contacts.

- There is an urgent need for preventive programs against drug abuse by young people.

- Dental disease, two-thirds of which is preventable, has received little attention.

* * *

Substantial progress has taken place in many areas of environmental health in the last decade. Public concern over air and water pollution has stimulated political interest and brought considerable money for control. But the problems are far from solved.

Although environmental factors are acknowledged as important determinants of health, we must also recognize that the human environment includes not only land, air and water but our home, work and recreational surroundings, transportation systems, food, drugs and all products we consume or use.

More knowledge is needed about the effects of additives and preservatives in our food. We must develop a greater concern over long-term effects of pesticides, as well as over methods of handling and processing foods. When California completes its Nutrition Survey early next year we will know

more about the nutritional status of Californians, including the problem of protein calorie deficiency which causes anemia and lowered resistance to infection.

In the next decade much more attention must be devoted to the factors in residential environment which are deterrents to good health, to community noise now recognized as an important environmental health problem, and to the prevention of accidents and injuries which take a large social and economic toll. Radical changes must be made in solid waste management, both to control land pollution and to conserve resources. We must guarantee healthful water and food supplies, the safety and efficacy of medicinal drugs, protection from radiation, occupational health and safety and vector control.

Public health, in short, must assume a leadership role in efforts to preserve and enhance overall environmental quality, no facet of which can be considered unrelated to health.

* * *

A most pressing need in the decade to come is to establish a more effective system for the delivery of comprehensive, high quality health care services to all Californians. Medicine and technology have far outstripped our ability to provide their benefits impartially to all people, rich or poor, black or white. This inadequacy is caused in part by a critical health manpower shortage. The State Health Department has taken a leading role in promoting training of health manpower, but ingenious and creative solutions to the shortage must be sought by health agencies throughout the state. The inequitable distribution of available manpower and the fragmentation in the total health care system also contribute to uneven application of health resources throughout the population.

Finally, we must take cognizance of the human and social aspects of medicine and public health. Instead of doing things for or to people, we must increasingly do things with them. We must seek the active and informed participation of the consumer in the distribution of health care services.

Attention, Pathologists

Jon V. Straumfjord, Jr., M.D., Ph.D., Professor and Chairman of the Department of Clinical Pathology and Clinical Pathologist in Chief, University Hospital, University of Alabama, will speak at the Pathology Section Meeting of the Annual Scientific Assembly, March 7th. Mark your calendar!

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

ALDES, JOHN HENRY, Los Angeles. Died 17 October 1969 in Los Angeles of heart disease, aged 63. Graduate of the University of Minnesota Medical School, Minneapolis, 1937. Licensed in California in 1946. Doctor Aldes was a member of the Los Angeles County Medical Association.

❖

BALL, WILLIAM H., Alhambra. Died 13 October 1969 in San Gabriel, aged 55. Graduate of the University of Colorado School of Medicine, Denver, 1940. Licensed in California in 1947. Doctor Ball was a member of the Los Angeles County Medical Association.

❖

BISHOP, JOY, (BLUM), Berkeley. Died 7 October 1969 in Berkeley of bronchiogenic carcinoma, aged 52. Graduate of Woman's Medical College of Pennsylvania, Philadelphia, 1947. Licensed in California in 1948. Doctor Bishop was a member of the Alameda-Contra Costa Medical Association.

❖

BOLOTIN, MAX THOMAS, Los Angeles. Died 9 October 1969 in Los Angeles of cardiac insufficiency, aged 67. Graduate of the University of Illinois College of Medicine, Chicago, 1925. Licensed in California in 1925. Doctor Bolotin was a member of the Los Angeles County Medical Association.

❖

CAMPBELL, CHARLES M., JR., Santa Barbara. Died 22 October 1969 in Santa Barbara, aged 57. Graduate of Harvard Medical School, Boston, 1937. Licensed in California in 1946. Doctor Campbell was a member of the Santa Barbara County Medical Society.

❖

CHARLTON, ALBERT TUTTON, Laguna Hills. Died 21 September 1969 in Laguna Hills, aged 87. Graduate of Rush Medical College, Chicago, 1909. Licensed in California in 1910. Doctor Charlton was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

❖

CLARK, GILBERT, Napa. Died 7 October 1969 in Vallejo of heart disease, aged 56. Graduate of the University of Southern California School of Medicine, Los Angeles,

1942. Licensed in California in 1942. Doctor Clark was a member of the Solano County Medical Society.

❖

FELDMAN, CARL, Los Angeles. Died 7 October 1969 in Los Angeles, aged 66. Graduate of the University of Oregon Medical School, Portland, 1928. Licensed in California in 1928. Doctor Feldman was a member of the Los Angeles County Medical Association.

❖

GILFILLAN, HAROLD M., San Francisco. Died 27 October 1969 in San Francisco, aged 68. Graduate of the State University of Iowa College of Medicine, Iowa City, 1925. Licensed in California in 1927. Doctor Gilfillan was a member of the San Francisco County Medical Society.

❖

GOUX, WARREN, Porterville. Died 4 October 1969 in Porterville of congestive heart failure, aged 52. Graduate of Wayne University College of Medicine, Detroit, 1943. Licensed in California in 1944. Doctor Goux was a member of the Tulare County Medical Society.

❖

HOLLENBECK, ARTHUR EARLE, Los Angeles. Died 17 October 1969 in San Diego of heart disease, aged 78. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1927. Licensed in California in 1927. Doctor Hollenbeck was a member of the Los Angeles County Medical Association.

❖

HUNSBERGER, HARVEY S., Petaluma. Died 23 October 1969 in Petaluma, aged 85. Graduate of Rush Medical College, Chicago, 1919. Licensed in California in 1919. Doctor Hunsberger was a retired member of the San Francisco County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

❖

KING, WALLIN WOODS, Los Angeles. Died 16 October 1969 in San Marino of coronary artery disease, aged 63. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1932. Licensed in California in 1932. M.D. degree from California College of Medicine, 1962. Doctor King was a member of the Los Angeles County Medical Association.

❖

LONGLEY, EARL GRANVILLE, Long Beach. Died 28 September 1969 in Long Beach of cardiac arrest, aged 73. Graduate of the State University of Iowa College of Medicine, Iowa City, 1924. Licensed in California in 1936. Doctor Longley was a member of the Los Angeles County Medical Association.

❖

MILLER, ROY ROBERT, Pasadena. Died 8 July 1969 in Pasadena of emphysema, aged 78. Graduate of the State University of Iowa College of Medicine, Iowa City, 1915. Licensed in California in 1926. Doctor Miller was a

retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



MOLZAHN, CLIFFORD D., Redlands. Died 29 September 1969 in Redlands of heart disease, aged 49. Graduate of the University of Minnesota Medical School, Minneapolis, 1952. Licensed in California in 1955. Doctor Molzahn was a member of the San Bernardino County Medical Society.



MONAGHAN, WILLIS ARTHUR, Seal Beach. Died 21 October 1969 in Long Beach of acute congestive heart failure, aged 73. Graduate of St. Louis University School of Medicine, St. Louis, 1920. Licensed in California in 1955. Doctor Monaghan was a member of the Los Angeles County Medical Association.



NAJJAR, CONSTANTINE CONRAD, Encino. Died 9 October 1969 in Van Nuys of pulmonary embolism-congestive heart failure, aged 62. Graduate of Rush Medical College, Chicago, 1934. Licensed in California in 1938. Doctor Najjar was an associate member of the Los Angeles County Medical Association.



ROBINSON, RUSSELL EUGENE, Long Beach. Died 29 September 1969 in Dover, Ohio, of coronary occlusion, aged 47. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1953. Licensed in California in 1954. M.D. degree from California College of Medicine, 1962. Doctor Robinson was a member of the Los Angeles County Medical Association.



SCHAEFER, JOHN HUGO, Los Angeles. Died 5 October 1969 in Los Angeles of myocardial infarction, aged 79.

Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1916. Licensed in California in 1916. Doctor Schaefer was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



STEFFY, JOHN L., Ramona. Died 26 May 1969 in Altadena, aged 79. Graduate of the University of Pittsburgh School of Medicine, Pittsburgh, 1911. Licensed in California in 1923. Doctor Steffy was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



STIER, HERBERT ALLAN, Los Angeles. Died 15 October 1969 in Los Angeles of an accidental gunshot wound, aged 33. Graduate of Stanford University School of Medicine, Palo Alto, 1960. Licensed in California in 1962. Doctor Stier was a member of the Los Angeles County Medical Association.



STOLZ, CHARLES E., Vista. Died 18 May 1969, aged 79. Graduate of Wisconsin College of Physicians and Surgeons, Milwaukee, 1911. Licensed in California in 1919. Doctor Stolz was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



SWAIN, CLAUDE R., Burbank. Died 12 October 1969 in Sepulveda of hepatic failure, aged 49. Graduate of University of Southern California School of Medicine, Los Angeles, 1945. Licensed in California in 1945. Doctor Swain was a member of the Los Angeles County Medical Association.

1970 ANNUAL SCIENTIFIC ASSEMBLY

of the California Medical Association

San Francisco, March 7-11

Topics of the three general meetings:

What is family practice?

Manpower — new aids to the physician

Systems of delivery for health care services

Renowned Speakers Are:

LYNN P. CARMICHAEL, M.D.

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University of Miami School of Medicine

JEROME POLLACK

Associate Dean for Medical Care Planning
Harvard Medical School

MIKE GORMAN

Executive Director
National Committee Against Mental Illness
Washington, D. C.

HENRY K. SILVER, M.D.

Professor of Pediatrics
University of Colorado Medical Center

EUGENE A. STEAD, JR., M.D.

Department of Medicine
Duke University Medical Center

L. HENRY GARLAND MEMORIAL LECTURE — MARCH 8

Guest Speaker: Melvin P. Judkins, M.D., Professor of Radiology and Director, Cardiovascular Laboratories, University of Oregon Medical School.

Title: "A Breakthrough in the Battle with Coronary Artery Obstructive Disease."

application for **HOTEL ACCOMMODATIONS**

NINETY-NINTH *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION • MARCH 7-11, 1970

SAN FRANCISCO HILTON HOTEL, SAN FRANCISCO

**HOUSE OF DELEGATES OPENING SESSION, HILTON HOTEL, SATURDAY EVENING, MARCH 7;
SCIENTIFIC SESSIONS, HILTON HOTEL, BEGIN SATURDAY NOON, MARCH 7**

1. Fill in the form below *completely* for room accommodations at the CMA's 1970 Annual Session. There are only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
 2. Your reservation request should include the definite date and hour of your arrival and departure.
 3. All reservations must be made through the CMA Housing Bureau, Suite 260, Fox Plaza, San Francisco, California 94102, by February 6, 1970.
 4. **CANCELLATIONS:** Please notify CMA Housing Bureau, Suite 260, Fox Plaza, San Francisco 94102 of all cancellations up to 15 days before Annual Session. Within last 15 days, make cancellations directly with hotel.
- CHANGES:** All other changes to be made directly with hotel at all times. Rooms will not be held after 6 P.M. unless a later arrival time has been requested. Failure to notify the hotel of any change in your arrival time may result in cancellation of your reservation.

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Suite 260, Fox Plaza, San Francisco, California 94102

Please reserve the following accommodations for the CMA's 1970 Annual Session in San Francisco, March 7-11.

Single Bedroom \$ Twin-Bedded \$ Double Bed \$ Suite \$

First Choice Hotel Second Third

Arrival (date) Hour ^{a.m.}_{p.m.} Departure (date) Hour ^{a.m.}_{p.m.}

THE NAME AND ADDRESS OF EACH HOTEL GUEST MUST BE LISTED. Include names and addresses of *each* person in a double or twin-bedded room, and names and addresses of *all other persons* for whom you are requesting reservations.

Your Name: Officer? Delegate? Alternate? Speaker?

Address: County

City and State Zip Code

GUESTS' NAMES AND ADDRESSES:

.....

.....

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Consultants for California Medicine in 1969

The editors wish to acknowledge with appreciation the valued services given by the following persons to the Journal during the past year.

Forrest Adams
John E. Adams
Paul M. Aggeler
William A. Atchley
Alfred Auerback
Ralph Audy

Allen Barbour
Wiley F. Barker
Eugene Barnett
Ernest Beutler
Edward Biglieri
F. William Blaisdell
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Joseph H. Boyes
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George Brecher
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Woman's Auxiliary to the CMA
Henry Work
David A. Wood
Edwin Wylie

Irwin Ziment

Attention, Dermatologists

Robert J. Gorlin, D.D.S., M.S., Professor and Chairman of the Division of Oral Pathology at the University of Minnesota School of Dentistry, will speak at the Dermatology Section Meeting of the Annual Scientific Assembly, March 8th. Plan to attend!

CONTINUING EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts
for Information

CMA:	California Medical Association Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
LLU:	Loma Linda University Contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
PMC:	Pacific Medical Center Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
STAN:	Stanford University Contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5940.
UCD:	University of California, Davis Contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0331.
UCI:	University of California — California College of Medicine, Irvine Contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
UCLA:	University of California, Los Angeles Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
UCSD:	University of California, San Diego Contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
UCSF:	University of California, San Francisco Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
USC:	University of Southern California Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

CANCER

January 5-10—**Pacific Cancer Conference.** American Cancer Society, Hawaii Division, Inc. at Hilton Hawaiian Village Hotel, Honolulu. Monday-Saturday. Reservations accepted on a first-come basis. Contact: H. Robert Bryman, Professional Consultants, Inc., 3194 Lawson Blvd., Oceanside, New York 11572.

January 24—**Problems in Head and Neck Cancer.** PMC. Saturday. Team approach by various specialists to decisions required in management of malignancies in the head and neck region. Radiation necrosis of the mandible; anesthesia—endotracheal intubation, hypotensive anesthesia; pitfalls; surgery of the head and neck tumors. \$40.

February 21-25—**Current Concepts in Cancer Chemotherapy.** UCLA at El Mirador Hotel, Palm Springs. Saturday-Wednesday.

MEDICINE

December 16—**Recent Developments in the Diagnosis of Contact Dermatitis.** UCSF at Hilton Hotel, San Francisco. Tuesday. Diagnostic techniques: use of patch testing, intradermal testing. The allergens: photo sensitizers, ointment base allergy, cosmetic allergy, topical medicaments allergy, newer industrial and chemical allergies. Testing for other environmental agents.

January 5-23—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three week course repeated six times through November, designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid-base metabolism, emphasis on practical techniques. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, Ext. 306.

January 10—**Coronary Care for Physicians and Nurses.** USC. Saturday.

January 13-14—**The American College of Cardiology—Annual Conference on Clinical Cardiology: New Developments in Diagnosis, Evaluation and Medical and Surgical Aspects of Therapy.** American College of Cardiology in cooperation with UCD and Sacramento Medical Center at Sacramento Medical Center, Sacramento. Tuesday-Wednesday. Designed for generalist, internist and cardiologist. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

January 14—**Seminar on Respiratory Diseases.** Tuberculosis and Respiratory Disease Association of Contra Costa at Holiday Inn, Concord. Wednesday 9-5:00. Didactic sessions and group seminars will cover allergic aspects of respiratory disease in children and adults, infectious respiratory disorders and the spectrum of chronic obstructive lung disease, film on spirometry. Contact: Mitchell Tarkoff, M.D., Chairman, Medical Education Committee, TB and Respiratory Disease Assoc. of Contra Costa, 105 Astrid Drive, Pleasant Hill 94523. (415) 935-0472.

- January 16-17—**Modern Trends in Epilepsy.** UCSF. Friday-Saturday. Critical analysis of team approach, epilepsy in childhood, re-appraisal of petit-mal, metabolic aspects of epilepsy and anticonvulsants, EEG and epilepsy, treatment of refractory epilepsy, neurosurgery of epilepsy, epilepsy and personality, focal epilepsy, epilepsy and the law, medical and social problems of epilepsy.
- January 16-18—**Total Rehabilitation—A Road to Work for "Unemployable" Cardiac Patients.** Ben R. Meyer Rehabilitation Center of Cedars-Sinai Medical Center at Sheraton-Universal Hotel, Los Angeles. Thursday-Sunday. Contact: John H. Aldes, M.D., Director, Ben R. Meyer Rehabilitation Center, 4833 Fountain Ave., Los Angeles 90029.
- January 17—**Workshop in Advanced Arrhythmias.** PMC. Saturday.
- January 20-31—**Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly through May, 1970. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitors, placement of pacing catheters, new aspects in diagnosis and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P. H., Administrative Associate, CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.
- January 21—**14th Annual Midwinter Symposium on Cardiovascular Research.** Los Angeles County Heart Association at the Hilton Hotel, Los Angeles. Wednesday. Contact: Joe Kennelley, Director, Public Information, LACHA, 2405 West 8th St., Los Angeles 90057. (213) 385-4231.
- February 2-3—**Symposium of Arrhythmias.** American College of Cardiology in cooperation with UCI at Newporter Inn, Newport Beach. Sunday-Tuesday. Latest anatomical, pharmacological, and physiological bases for disturbances of cardiac rhythm related to specific disease entities and situations. Workshops will demonstrate clinical application of basic concepts. Contact: UCI.
- February 3-14—**Coronary Care Unit Program for Physicians.** CRMP Area V. See January 20-31.
- February 6—**Stroke Symposium.** CRMP Area VII at Hotel Del Coronado, Coronado. Friday. \$10. Contact: Derek W. Price, Assoc. Coordinator, CRMP Area VII, 7816 Ivanhoe, La Jolla 92037. (714) 459-3739.
- February 12-13—**Aplastic Anemia.** UCSF. Thursday-Friday.
- February 13-14—**American College of Physicians — Northern California-Nevada Regional Meeting.** Mark Thomas Inn, Monterey. Friday-Saturday. Contact: John R. Gamble, M.D., Governor, No. Calif. and Nevada Region, ACP, 655 Sutter Street, San Francisco 94102. (415) 673-4080.
- February 14-15—**Arthritis Symposium.** USC at Childrens Hospital, Los Angeles. Saturday-Sunday.
- February 17-18—**American College of Physicians — Hawaii Regional Meeting.** Pacific Club, Honolulu. Tuesday-Wednesday. Tuesday and Wednesday a.m.: Scientific Sessions. Tuesday p.m.: Lecture in connection with The American College of Surgeons, "What's Left in Thyroid Disease for the Surgeon?" Contact: Morton E. Berk, M.D., Governor, Hawaii Region, ACP, 1133 Punchbowl Street, Honolulu 96813.
- February 18—**Coronary Heart Disease, 1970.** USC at Huntington-Sheraton Hotel, Pasadena. Wednesday. Latest research and clinical information on diagnosis and management of coronary disease. Prevention and post-coronary rehabilitation. \$35.
- February 20-21—**American College of Physicians — Southern California Regional Meeting.** Coronado. Friday-Saturday. Contact: Eugene Braunwald, M.D., Chairman of Scientific Program, UCSF.
- February 28-March 1—**Your Patient with Renal Disease.** UCSF at Franklin Hospital, San Francisco. Saturday-Sunday.
- March 2-20—**Coronary Care for Physicians Training Program.** CRMP Area IV. See January 5-23.
- March 3-14—**Coronary Care Unit Program for Physicians.** CRMP Area V. See January 20-31.
- March 5-6—**Endocrine Disease.** USC at Century Plaza Hotel. Thursday-Friday.
- March 5-6—**Dialogues in Dermatology.** UCSF at Sir Francis Drake Hotel, San Francisco. Thursday-Friday. Veterinary dermatology; atopic dermatitis. The Perineum: vulvar dermatology; genito-urinary dermatology; proctologic dermatology; stomatology and the dermatologist; oto-dermatology; blepharitis; current advances in burn therapy; podiatric dermatology; stasis dermatitis and ankle ulcers; research dermatology.
- March 14—**Auscultation of the Heart.** PMC. Saturday. Discussion and teaching on the heart sound simulator.
- March 26—**Obesity.** USC at Hilton Hotel, Los Angeles. Thursday.
- April 3-4—**Annual Symposium on Cardiovascular Disease.** Sacramento-Yolo-Sierra Heart Association at Sacramento Inn, Sacramento. Friday-Saturday. Contact: Harold S. Hunt, Exec. Dir., Sacramento-Yolo-Sierra Heart Assoc., 1010 25th St., Sacramento 95816. (916) 444-8650.
- April 4-5—**Armchair Allergy.** PMC. Saturday-Sunday. Early diagnosis, role of steroids in management of asthma, skin tests, current concept of the basic steps in the allergic reaction.
- April 6-15—**Cardiology for the Consultant—A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. Ten day program for well-trained clinicians to sharpen ability in the field of cardiology. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.
- April 8-9—**Medical Surgical Gastroenterology.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday.
- April 10—**Annual Symposium on Heart Disease.** Orange County Heart Association at Disneyland Hotel, Anaheim. Friday. Contact: Liggett McLaws, Program Dir., OCHA, P.O. Box 1704, Santa Ana 92702. (714) 947-3001.
- April 11—**Myocardial Infarction.** PMC. Saturday.
- April 11-12—**Clinical EMG.** UCSF. Saturday-Sunday.
- April 22-25—**Advances in Endocrinology and Metabolism.** UCSF. Wednesday-Saturday. Intensive review

of interrelationships between metabolic disease and endocrine dysfunction, critical evaluation of new developments.

Continuously—Basic Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

Grand Rounds—Medicine

Tuesdays

9-10:30 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Wednesdays

Grand Rounds in Internal Medicine. 10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.
11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

Grand Rounds in Internal Medicine. 12:30-1:30 p.m., University Hospital, UCSD.

Grand Rounds in Internal Medicine. 1:30-3:00 p.m., Fresno General Hospital.

Thursdays

10:30-12:00 noon, Room C3-105, UCLA Medical Center. UCLA.

Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

2-3:00 p.m., Classroom, Third Floor, Fresno General Hospital, Fresno. CRMP Area IV.

Rheumatology Grand Rounds. 11:30 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

OBSTETRICS AND GYNECOLOGY

February 20-21—**Birth Prevention: The Growing Challenge to Physicians and to the Community.** UCSF. Friday-Saturday.

PEDIATRICS

February 7—**Pediatric Urology—The Dilated Ureter; The Uncoordinated Bladder.** UCSF at Childrens Hospital, San Francisco. Saturday. The dilated ureter: mechanics of dilatation, diagnostic techniques, hydro-ureter and reparative ureteral surgery, treatment. The uncoordinated bladder. \$25.

February 9-20—**Mental Retardation.** UCLA in cooperation with Pacific State Hospital, Pomona, at UCLA

Neuropsychiatric Institute. Two weeks. For physicians and allied professionals. Causation, symptomatology, care, treatment and management, diagnostic techniques suitable for office practice, parental reactions and intra-family psychopathology, and recent research findings. Contact: UCLA.

March 7—**Pediatric Hematology.** UCSF at Childrens Hospital and Adult Medical Center, San Francisco. Saturday.

March 13-14—**Child Neurology: Recent Advances.** UCSF. Friday-Saturday. Review of neurological examinations and procedures, paroxysmal neurological disorders, metabolic problems in pediatric neurology, disorders of movement.

March 20-21—**Pulmonary Disease in Newborns.** UCI, CRMP Area VIII in cooperation with the National Cystic Fibrosis Research Foundation at Childrens Hospital of Orange County. Friday-Saturday. Registration by March 1 is necessary. Contact: Bruce D. Ackerman, M.D., Dept. of Pediatrics, UCI.

March 23-26—**Clinical Evaluation of Children with Learning Disorders.** UCSF. Monday-Thursday. Discussions and demonstrations of the total clinical evaluation: pediatric, ophthalmologic, speech, audiology and educational factors.

Grand Rounds—Pediatrics

Tuesdays

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Conference Room, Sixth Floor, Harbor General Hospital, Torrance. CRMP Area IV.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Stanford University Medical Center, Palo Alto.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

PSYCHIATRY

January 7-March 11—**Group Methods.** UCSF at V.A. Hospital, San Francisco. Wednesdays 11:30 a.m.-1:00 p.m. For physicians and para-professionals in the mental health field. Various aspects of group psychotherapy: personal experience in group process, role

playing, group treatment and the generation gap, couples, family, adolescent and marathon groups and color marathon racial confrontation. \$25 full program, \$2 individual lectures.

March 14-15—**Current Theories in Psychiatry.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

March 14-15—**The Troubled Adolescent in the Modern Family.** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

March 20-21 — **Suicide Prevention and Advanced Workshop.** UCSF. Friday-Saturday.

March 23-26—**American Orthopsychiatric Association.** Mark Hopkins and Fairmont Hotels, San Francisco. Monday-Thursday. Contact: Marion F. Langer, Ph.D., AOA, 1790 Broadway, New York 10019.

April 1-June 3—**Group Methods.** UCSF at V.A. Hospital, San Francisco. Wednesdays. Weekly lectures and participants assigned to clinic groups.

April 4-5—**The Brain and Behavior.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday. New developments in chemistry, neuroanatomy, and neurophysiology related to human behavior.

April 18-19—**New Approaches to the Care of the Suicidal Patient.** UCLA. Saturday-Sunday.

RADIOLOGY—PATHOLOGY

January 31-Feb. 1—**Los Angeles Radiological Society—22nd Annual Midwinter Radiological Conference.** International Hotel, Los Angeles. Saturday-Sunday. Diagnosis, therapy, and nuclear medicine. \$30. Contact: Arthur F. Schanche, M.D., 8618 So. Sepulveda, Suite 100, Los Angeles 90045.

March 1-6—**American Radium Society.** Hotel del Coronado, Coronado. Sunday-Friday. Contact: John V. Blady, M.D., Secretary, ARS, 2201 Benjamin Franklin Parkway, Philadelphia 19130.

March 3-7—**Diagnostic Radiology.** UCSF. Tuesday-Saturday. Primarily for residents in radiology. Radiological physics, with attention given to the requirements of the American Board of Radiology.

April 1-5—**Cytology for Pathologists and Cytotechnologists.** UCSF at St. Francis Hotel, San Francisco. Wednesday-Sunday. Intensive study in the techniques and interpretation of cytologic specimens. Appropriate separations for the respective fields.

April 17-30—**Gastrointestinal Radiology.** USC, Princess Carla Cruise to Mexico from Los Angeles. Two weeks.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

SURGERY—includes Anesthesiology

January 10-11—**Psychiatric Implications of Newer Surgical Horizons.** UCSF at Sutter Memorial Hospital, Sacramento. Saturday-Sunday. Surgeon's view of heroic surgery; transplantation, the impact on the patient; psy-

chiatric problems in the intensive care unit; the problem of mutilation and repair; total care of the patient.

January 12-16—**Otologic Surgery.** Los Angeles Foundation of Otology and USC in cooperation with St. Vincent's Hospital at St. Vincent's Hospital, Los Angeles. Monday-Friday. One day will be devoted to otosclerosis surgery, three days to surgery of chronic ear disease. One day devoted to inner ear problems, glomus tumors, and facial nerve paralysis. \$300. Contact: Glenn Snyder, Managing Director, Los Angeles Foundation of Otology, 2130 W. Third St., Los Angeles 90057.

January 17-18—**Cadaver Course.** Research Study Club of Los Angeles at USC. Saturday 2-5 p.m.; Sunday 9 a.m.-3 p.m. Surgical Anatomy of the Orbit and Adnexa, Individual Dissection. Limited to 20 applicants attending the Thirty-Ninth Annual Mid-Winter Convention in Ophthalmology and Otolaryngology. \$50. Contact: Burns C. Steele, M.D., Secretary, Research Study Club of Los Angeles, 1411 W. Olive Ave., Burbank 91506. (213) 846-3614.

January 19-23—**Research Study Club of Los Angeles—39th Annual Mid-Winter Convention in Ophthalmology and Otolaryngology.** Statler Hilton Hotel, Los Angeles. Monday-Friday. Simultaneous lectures in Otolaryngology and Ophthalmology. \$100. Contact: Burns C. Steele, M.D., Secretary, Research Study Club of Los Angeles, 1411 W. Olive Ave., Burbank 91506. (213) 846-3614.

January 23-25—**Pediatric Anesthesiology—8th Annual Clinical Conference.** Childrens Hospital of Los Angeles. Friday-Sunday. Pre-anesthetic evaluation, methods of induction, choice of agent, pharmacology, iatrogenic diseases, and postoperative care. \$75. Contact: Wayne Herbert, M.D., Division of Anesthesiology, Childrens Hospital of Los Angeles, P.O. Box 54700, Los Angeles 90054.

January 26-30—**Techniques in Nasal Surgery.** UCLA. Monday-Friday. Observation of dissection of cadaver material and videotaped surgical procedures. Patient selection; photography—pre- and post-operative; facial analysis; basic rhinoplasty; hump removal—lateral and medial osteotomies; lobule techniques; nasal physiology; surgical techniques; septal surgery; complications of rhinoplasties grafts; trauma—nasal and ear; otoplasties; synthetic injections.

February 1-4 — **Surgical Anatomy.** LLU. Sunday-Wednesday. \$150.

February 7 — **Surgical Emergencies.** PMC. Saturday 8-4:30. Morning session: Monitoring and Management of Shock. Afternoon: Selected and control problems, workshop including case studies and exercises involving blood and gas data, venous pressures.

February 25-March 1—**Controversial Areas in Surgery.** UCLA at El Mirador Hotel, Palm Springs. Wednesday-Saturday. \$125.

March 14-15—**Techniques of Surgery of the Foot.** UCLA. Saturday-Sunday.

March 19-21—**Medical Ophthalmology.** UCSF. Thursday-Saturday.

March 25-28—**Neurosurgical Society of America.** Ojai Valley Inn, Ojai, Calif. Wednesday-Saturday. Contact: William F. Collins, M.D., Secretary, NSA, 789 Howard Avenue, New Haven, Conn. 06510.

April 8-9—**Medical Surgical Gastroenterology.** See Medicine, April 8-9.

April 9-10—**General Surgery.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

Grand Rounds—Surgery

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

9:30 a.m., Neuroradiology; 10:15, Neurology; 11:15, Neurosurgery. Neurology Conference Building 7, V.A. Hospital, Palo Alto. STAN.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

OF INTEREST TO ALL PHYSICIANS

CMA Postgraduate Institutes and Circuit Courses

January 24—**West Coast Postgraduate Course, San Luis Obispo.** CMA and UCI at Sierra Vista Hospital and San Luis Obispo General Hospital. Saturday. Enzymes diagnosis and thyroid treatment. \$10. Contact: CMA.

January 29-30 — **Southern Counties Regional Postgraduate Institute.** CMA, STAN, and Southern Counties Medical Societies at El Mirador Hotel, Palm Springs. Thursday-Friday. Thursday a.m.: Acute Injuries of Hand and Face, Acute Cardiac Emergencies and Their Management. Thursday afternoon: The Comatose Patient, Acute Urological Problems. Friday a.m.: Acute Emergencies in the Infant and Child, Shock, Cranial and Spinal Cord Injuries, Acute Pulmonary Problems. Friday afternoon: Symposium on the Multiple Injured Patient. Contact: CMA.

February 9, 10, 11-March 2, 3, 4 — **Annual Postgraduate Circuit Courses — Spring Session.** CMA and STAN at Mt. Shasta Community Hospital; Enloe Memorial Hospital, Chico; and Auburn Faith Hospital, Auburn. Radiotherapy and Cancer Management, Depression — Disease and Symptom, Pathology—Past, Present and Future, and Injuries of the Hand and Face. \$20 for Spring Series. Contact: CMA.

April 2-3—**West Coast Counties Regional Postgraduate Institute.** CMA, UCD and Monterey County Medical Society at Del Monte Hyatt House, Monterey. Thursday-Friday. Contact: CMA.

January 2-4—**Medicine and Law.** The American College of Physicians and USC Division of Postgraduate Psychiatry at USC. Friday-Sunday. Of special interest to physicians in clinical hospital administrative and teaching roles. Broad overview of significant interface between medicine and law, both theoretical and practical. Medical malpractice will not be a major consideration. \$60 for ACC members, \$100 for nonmembers. Contact: Donald H. Naftulin, M.D., Director, Postgraduate Psychiatry, USC.

January 6-March 24—**Psychiatric Principles in a Medical Practice.** USC Division of Postgraduate Psychiatry at General Hospital of Ventura County. Tuesdays 7:30-9:30 p.m. \$35. Contact: Ronald A. Markman, M.D., Assistant Dir., Postgraduate Psychiatry, USC.

January 8-9—**Drug Therapy.** UCSF. Thursday-Friday. Newest therapeutic developments, the infectious states, acute cardiovascular insults, degenerative cardiovascular states.

January 15-16—**New and Old Antibiotics.** USC. Thursday-Friday.

January 19-30—**Intensive Review for Family Practice.** USC. Two weeks. Geared for the individual in general or family practice. Comprehensive review of basic principles, new concepts of disease. \$150.

January 20-April 7—**Psychiatric Principles in a Medical Practice.** USC Division of Postgraduate Psychiatry at South Coast Community Hospital Auditorium, South Laguna. Tuesdays. \$35. Contact: Ronald A. Markman, M.D., Assistant Dir., Postgraduate Psychiatry, USC.

January 21-23—**Hyperbaric Medicine and Allied Topics.** The Hospital of the Good Samaritan Medical Center, Los Angeles. Wednesday-Friday. Contact: John M. Workman, M.D., Dir., Hyperbaric Unit, The Hospital of the Good Samaritan Medical Center, 1212 Shatto Street, Los Angeles 90017.

January 21-April 29—**Clinical Psychiatry for Non-Psychiatrists: A Course in Medical Psychotherapy.** UCSF. Wednesdays 1-5:00. Open to physicians and paramedical specialists, enrollment limited to 14. Weekly interviews with psychiatric patients, supported by individual hours of faculty consultation and joint treatment reviews of all patients and seminars. Seminars will cover diagnosis and management of psychiatric emergencies, psychiatric illness in children, testing, and community psychiatry. \$25.

January 25—**What Insurance Is All About, A Symposium for Medical Assistants.** UCSF. Sunday.

January 26-March 6 — **Mission Orientation Program.** LLU and LLU School of Public Health. Six week program to include tropical medicine, personal health and tropical hygiene, cultural anthropology, practical linguistics, dynamics of interpersonal relationships, seminar discussion by veteran missionaries and others with overseas experience, opportunity to study other areas of personal interest. \$175. Contact: Herschel C. Lamp, M.D., Dir., Mission Orientation Program, School of Public Health, LLU.

January 30-Feb. 1 — **Financial, Tax, and Investment Planning.** UCLA. Friday-Sunday.

January 31-February 1 — **Eighth Scientific Seminar Program.** Memorial Hospital of Southern California,

Memorial Hospital of Gardena, and Brotman Foundation of California at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Coma, Adolescent Medicine and Chaos, The Patient with Disordered Blood Coagulation, Arthritis—1970. \$15. Contact: David M. Brotman, M.D., Secretary, Seminar Committee, Memorial Hospital of Southern California, 3828 Hughes Ave., Culver City 90230. (213) 834-3111.

February 6-8—**Drug Abuse.** UCSF at Sea Gull Inn, Mendocino. Friday-Sunday. Historical aspects, marijuana, alcoholism, stimulants and depressants, hallucinogens and the psychedelic experience, narcotic addiction, changing patterns of drug abuse, sociological and cultural factors. \$15.

February 7—**Suicide.** UCSF. Saturday 9-4:30. Degrees of responsibility in suicide; individual, religious, social, legal, and accidental aspects.

February 7-8—**Los Angeles Obstetrical and Gynecological Forum—19th Annual Meeting.** Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Saturday: the fetus in jeopardy, infections in obstetrics and gynecology. Sunday: 1970 Ob. and Gyn. Assembly. Contact: Dee Davis, Executive Sec., L.A. Ob. & Gyn. Soc., 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

February 11-12—**Critical Care Medicine and Circulatory Shock.** USC. Wednesday-Thursday. For the practitioner, internist, general surgeon and surgical specialist. \$50.

February 11-13 — **Course for Physicians in General Practice.** UCSF at Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Geriatrics; allergy; endocrinology; cardiovascular topics; pediatrics; elective sessions in anesthesiology, basic electrocardiography, vector approach; rehabilitation in strokes and other neurological diseases; clinical workshops.

February 14—**Cardiac Emergencies.** PMC. Saturday. Therapy of intractable heart failure, modern concepts of shock, and emergencies arising in the infant.

February 15—**Hollywood Community Hospital Annual Symposium.** Sheraton-Universal Hotel, Hollywood. Sunday. Contraceptive and Sexual Problems. Contact: Viola Kindstrand, Symposium Secretary, Hollywood Community Hospital, 6245 de Longpre Ave., Hollywood 90028. (213) 462-2271.

February 15-19—**Loma Linda University School of Medicine, Alumni Association—Postgraduate Convention.** Ambassador Hotel, Los Angeles, and LLU. Sunday-Thursday. Sunday-Monday: Refresher course, LLU. Tuesday-Thursday: Scientific Assembly, Ambassador Hotel. Contact: Samuel H. Fritz, M.D., General Chairman, Alumni Postgraduate Convention for 1970, LLU.

February 26-April 30—**Teaching Clinics in Psychiatry.** UCLA. Thursdays.

February 27-28—**The Physician and Athletics.** UCSF. Friday-Saturday.

February 28—**Problems in Social Change Reflected in Medical Practice.** UCSF at Herrick Memorial Hospital, Oakland. Saturday.

March 7-11—**California Medical Association—Annual Scientific Assembly.** Hilton Hotel, San Francisco.

Saturday-Wednesday. General Sessions: Saturday p.m.: Family Practice. Sunday p.m.: Manpower. Monday p.m.: Systems of Delivery. Tuesday p.m.: Birth Defects. Guest Speakers for General Sessions include: Lynn P. Carmichael, M.D., University of Miami School of Medicine; Mike Gorman, National Committee Against Mental Illness; Jerome Pollack, Associate Dean for Medical Care Planning, Harvard Medical School; Henry K. Silver, M.D., Professor of Pediatrics, University of Colorado Medical Center; Eugene A. Stead, Jr., M.D., Duke University Medical Center. Assembly includes special conferences, section meetings, and medical motion picture symposia daily. More complete program listing in January pre-convention issue.

March 19-20 — **Postgraduate Seminar and Clifford Sweet Memorial Lecture.** Childrens Hospital of Oakland. Thursday-Friday. Sex Education for Physicians. Contact: Inetta Carty, Childrens Hospital of Oakland, 51st and Grove Streets, Oakland 94609. (415) 654-5600.

March 25-26 — **Los Angeles County Heart Association and Los Angeles Academy of General Practice—Seventh Annual Spring Symposium for Physicians Practicing General Medicine.** Wednesday-Thursday. Contact: Joe Kennelly, Director, Public Information, LACHA, 2405 W. Eighth Street, Los Angeles 90057. (213) 385-4231.

April 11-12 — **Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton. Saturday-Sunday.

April 17-18—**Infectious Diseases.** UCSF at Childrens Hospital, San Francisco. Friday-Saturday. For pediatricians, family physicians, internists and clinically oriented bacteriologists.

April 19—**Office Emergencies: A Symposium for Medical Assistants.** UCSF. Sunday.

April 25-26—**Comparative Medicine.** UCSF. Saturday-Sunday. Professionals in the fields of veterinary medicine, pediatrics, public health and microbiology.

April 25-26—**Sex in Modern Society.** UCSF at Flamenco Motor Hotel, Santa Rosa. Saturday-Sunday.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

TELEVISION

Southern California's Medical Television Network. UCLA. Weekly broadcasts, Tuesdays 8:30 a.m. Contact: UCLA Medical Television Network.

December 16—**Aggressive Management of the Stroke Patient, Part III.** Rehabilitation and Discharge Planning. UCI, California College of Medicine.

December 23—**Tumors of the Head and Neck, Part I.** Carcinoma of the Lip, Oral Tongue and Floor of the Mouth. Washington-Alaska Regional Medical Programs.

January 6—**Tumors of the Head and Neck, Part II.** The Asymptomatic Neck Mass. Washington-Alaska Regional Medical Programs.

January 13—**Tumors of the Head and Neck, Part III.** Carcinoma of the Larynx. Washington-Alaska Regional Medical Programs.

January 20—**Post Hospital Care of the Cancer Patient.** UCLA and City of Hope National Medical Center.

January 27—**Use and Abuse of the X-Ray Department.** University of Western Ontario, Canada.

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Attention, Anesthesiologists

Joseph J. Buckley, M.D., Professor of Anesthesiology at University of Minnesota Hospital, will speak at the Anesthesiology Section Meeting of the Annual Scientific Assembly, March 8th. Plan to attend!

BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

PROGRESS IN CLINICAL PSYCHOLOGY — Volume VIII — Dreams and Dreaming — Edited by Lawrence Edwin Abt, Ph.D., and Bernard F. Riess, Ph.D. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 192 pages, \$9.75.

The topical areas of sleep, dreaming, and suggestion are exciting fields of research in which the authors have selected outstanding contributors to present up-to-date findings on subject areas which have long been studied mainly through introspection and other non-scientific approaches.

The nature of sleep is well documented from a measurement point of view, with findings sufficiently detailed to stimulate the well informed reader; yet equally understandable by those readers less informed on such aspects as the stages of sleep and dreaming represented in EEG patterns. The effects of dream deprivation are presented with many practical and theoretical questions raised. For example, "What is the function of REM sleep and how does such deprivation affect behavior measurement in man as well as psychological test performance?" While the data are not conclusive and while suggestions for more comprehensive research studies are presented, there is evidence that loss of REM sleep does contribute to observed and measured decrement in performance. The effects of such loss on general social and emotional behavior are well documented and likened to the effects of concentration camp and prisoner of war experiences, with sleep deprivation leading to psychotic-like perceptual and cognitive changes.

States of sleep disorders in children are presented, relating such anomalies as somnambulism, enuresis, and night terrors to "first third of the night and stage four sleep." Other papers discuss relationships between dream states and varied psychophysiological measures such as ectodermal responses (no longer GSR), electromyographic studies, and fluctuations in penile erections. The findings, although inconclusive, are presented as motivation for further research to test the hypothesis that there is a psychophysiological parallel to the dream state.

Clinical and psychoanalytic implications of dream research are reviewed, exploring relationships between repression and forgetting of dreams; dream recall, hypnagogic reverie findings; and deliberate manipulation of dream content through a variety of experimenter imposed conditions. In addition, the effects of psychoactive and tranquilizing drugs reflected in experimental and literary findings are presented. The suppression of REM sleep with sedation and the change in sleep patterns and dreaming under drugs have relevance to physicians in general and is seen as an important concomitant to be considered in patient care and management.

Of international significance is the research from the U.S.S.R. with waking, sleep, and hypnotic suggestion. Mathematical models for assessing the potency of sugges-

tion are presented. "The basic mechanism of suggestibility was seen in the functional separation of the activity of the cortex," where fatigue states contribute to a lowering of the "tonus of the cortex" and thus lead to an increase of suggestibility.

In summary, *Progress in Clinical Psychology*, Volume 8, 1969, has presented empirical and experimental data highly relevant to the expanding international interest in the broad area of states of consciousness and awareness. The literature reviews by the contributing authors, the excellence of the selected articles, and the continuing demonstration of a scientific approach to the study of such subjective states as sleep, dreaming, and suggestion, are all exciting demonstrations of the expanding areas of methodological study in the broad field of "Psychology."

MORRIS J. PAULSON, Ph.D.

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THE OPHTHALMIC ASSISTANT — FUNDAMENTALS AND CLINICAL PRACTICE — Harold A. Stein, M.D., M.Sc. (Ophth.), F.R.C.S.(C), Clinical Teacher, University of Toronto; Chief, Department of Ophthalmology, Scarborough General Hospital; Attending Ophthalmologist, Mount Sinai Hospital and Sunnybrook Hospital, Toronto; Chairman, Section on Ophthalmology, Ontario Medical Association, Director, Association of Ophthalmic Assistants of Ontario; and Bernard J. Slatt, M.D., F.R.C.S.(C), Clinical Teacher, University of Toronto; Attending Ophthalmologist, Scarborough General Hospital, Toronto General Hospital, and Branson Hospital; Director, Association of Ophthalmic Assistants of Ontario, both Ontario, Canada. The C. V. Mosby Company, Publishers, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1968. 406 pages, 550 illustrations, \$19.50.

This excellent book should be required reading for all those who assist the ophthalmologist in the examination of patients, performance of diagnostic and therapeutic office procedures, and the care of hospitalized patients both on the wards and in the operating room. It fills a long felt need.

The role of para-medical personnel in the care of ophthalmic patients is increasing in importance. Many examination techniques are delegated to assistants, many of whom must learn these techniques from on-the-job experience. The training of lay technicians takes time and patience. This book should make the task much easier for both teacher and trainee.

The book is divided into five parts as follows:

1. Basic sciences, including anatomy, physiology, optics and pharmacology.
2. Clinical practice, dealing with methods and equipment used in eye examination, facts about glasses, injuries and emergencies, office surgery, the operative patient and the glaucoma patient.
3. Special procedures, such as tonography, orthoptics, low-vision aids, and photography.
4. Community ocular problems such as eye screening programs, public relations and the blind.

5. An atlas of common eye disorders.

Each section treats its subject thoroughly and well. The portion on clinical practice is by far the most comprehensive and detailed in presentation. The illustrations, format and printing are uniformly excellent.

DAVID O. HARRINGTON, M.D.

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ATLAS OF NUCLEAR MEDICINE—Volume 1—Brain—Frank H. Deland, M.D., Assistant Professor of Radiology, Johns Hopkins Medical Institutions; and Henry N. Wagner, Jr., M.D., Professor of Radiology and Radiological Science, Associate Professor of Medicine, Johns Hopkins Medical Institutions; with the assistance of Wendy A. North, M.I.R., Research Assistant, Johns Hopkins Medical Institutions. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 217 pages, \$18.00.

The first atlas of nuclear medicine published appears to be in a "hard act to follow" category. Doctors Deland and Wagner and their several assistants who cooperated in the technical, artistic, and photographic preparation of the material in this volume are to be congratulated on their generally effective presentation. Gamma images are presented with pertinent anatomic, physiologic and pathologic supporting information. All case material is presented with a brief clinical description, diagnostic impressions prior to radiopharmaceutical distribution imaging, and a description of the gamma images with their interpretation. Subsequent course and final diagnosis are then presented. This strong clinical orientation should prove to be particularly useful for the student surveying brain imaging procedures.

The particularly effective sections on cerebrovascular diseases, posterior fossa tumors, and cisternography should be read by any serious student of nuclear medicine techniques. The section on cerebrovascular diseases is notably well conceived and often original, identifying more specific vascular localization of labeling abnormalities than is usually accomplished with scanning or gammaphotography techniques.

The authors' foreword states that the purpose of the atlas is "to portray the images obtained by scanning." My major criticism would be to note the lack of sufficient information on scintiphotography or gammaphotography. There are relatively few scintiphotos illustrated and few of those illustrated are shown in the conventional Polaroid format of white information on a black background. Most of the gammaphoto illustrations are shown as negative exposures with black information on a white background. This also provides a broader exposure range and less inherent background cutoff in the film than with Polaroid film. A major deficiency of the atlas, in my opinion, is the complete lack of any information on cerebral angiography and perfusion imaging studies with radiopharmaceuticals. The gamma camera has certainly made very definite contributions in this area, providing a safe and readily performed angiographic type study which contributes materially to the diagnosis of the subsequent static scintiphotos or scans. In line with the authors' emphasis on scanning, all the gamma images are presented in a format which is larger than is justified by the information density in the images and the reader's arm length. Image minification is a well established technique of improving diagnostic efficiency in nuclear medicine and smaller images would seem appropriate for this atlas. Presentation of the larger pictures has required that many comparison views be eliminated, and this is a drawback, since comparison views are so much a part of gamma image interpretation, both for scans and for gammaphotos. Conventional scans are generally presented as high contrast images with appreciable background cutoff so as to emphasize pathologic details. This is entirely

suitable for an atlas and allows ready identification of abnormalities in most of the illustrations.

It was a pleasant surprise to see that Doctor Wagner has lessened somewhat his initial resistance to clinical use of gammaphotography as a basic technique for acquiring radioisotope distribution data *in vivo*. I would predict that the next edition of this atlas will include dynamic scintillation camera studies and will give increasing attention to scanning techniques that employ very sharply focused collimation with narrow range of focal depth to produce scans which are more planographic than those that are customarily used for screening for intracranial lesions at present. This text is a major contribution to teaching brain scan (and gammaphoto) interpretation and will serve our students well.

MALCOLM R. POWELL, M.D.

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ALCOHOL AND THE IMPAIRED DRIVER—A MANUAL ON THE MEDICOLEGAL ASPECTS OF CHEMICAL TESTS FOR INTOXICATION—Committee on Medicolegal Problems, American Medical Association. American Medical Association, 535 North Dearborn Street, Chicago, Ill. (60610), 1968. 234 pages, \$1.50 per copy (with discounts on orders for 16 or more).

In 1965 the 80,000,000 automobiles in the United States were involved in accidents that killed 49,000 persons and injured 3½ million persons. Based on these figures the predicted 113,642,000 cars in 1975 will kill 75,000 persons and injure over five million. Up to 50 percent of these accidents are related to the use of alcohol. These grim statistics do and will continue to involve the time and energies of the medical profession. It is imperative that physicians learn more about alcoholism and its relationship to auto accidents. This book answers many questions in this field and points the direction medicine, society and the law must go in the years ahead.

Some drivers are impaired with a blood level of 0.04 percent, most are impaired at 0.08 percent. At levels of 0.10 percent there is severe, significant and dangerous deterioration in driving abilities. Alcohol levels in the body may be tested by sampling blood, breath or urine. These are the most commonly tested materials although alcohol may be measured in saliva, vomitus, cerebrospinal fluid, stomach contents, or body tissues. Alcohol is eliminated from the body at a constant rate. There is no way to speed up detoxification. Central nervous system depressants such as tranquilizers, narcotics, or barbiturates potentiate the effect of alcohol.

In 1939 the American Medical Association stated that blood levels under 0.05 percent did not indicate drunkenness while levels of 0.15 percent did indicate that the person was under the influence of alcohol. Blood levels between 0.05 percent and 0.15 percent might or might not indicate that the individual was under the influence of alcohol, depending on other factors. However since 1960 the American Medical Association has held that blood levels of 0.10 percent be accepted as *prima facie* evidence of alcoholic intoxication, recognizing that many individuals are under the influence of alcohol in the 0.05 percent to 0.10 percent range. In 1962 the American Medical Association recommended that reporting of alcohol concentration in the blood be on the basis of milligrams of alcohol per 100 milliliters of blood. Thus 0.05 percent is 50 milligrams per 100 milliliters (50mg/100ml).

The National Highway Safety Act of 1966 requires the states to evaluate the relationship between alcohol and auto accidents including laws, enforcement methods, treatment of alcoholism and other aspects. In most states a blood level of 0.15 percent is presumptive of alcoholism: 11 have set the presumptive level at 0.10 percent and

Utah has established 0.08 percent as the presumptive level. Many of the states have implied consent laws whereby the driver who refuses to submit to chemical tests in circumstances where the test is authorized may have his license to drive suspended or revoked.

While many drivers involved in driving accidents have high blood alcohol levels, young, inexperienced drivers may have accidents with low blood levels. It is estimated that one-third of United States adults will drink and drive at some time during the year. The average person attending a cocktail party rarely has a blood alcohol level over 0.05 percent. However, two or more drinks taken in less than an hour may elevate the blood alcohol to the level of legal intoxication. The over-eager host pushing drinks on his guests may grossly impair their driving skill and inadvertently lead to arrest for drunken driving.

This small book contains a wealth of information for a very nominal sum. It includes chapters on Alcohol and Traffic Safety, Acute Alcoholic Intoxication, Pharmacology and Toxicology of Alcohol, Effect of Alcohol on the Nervous System, Effect of Alcohol on Driving Ability, Chemical Tests, Measures for Control of Drinking Drivers, Medical-legal Aspects, Constitutional Aspects of Chemical-test Evidence, Medical-legal Aspects of Chemical Tests and an appendix of court decisions and scientific references.

As a reference book on drinking and driving it is clearly the best available. For any physician who wishes factual material on this subject it is highly recommended.

ALFRED AUERBACK, M.D.

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REVIEW OF MEDICAL PHARMACOLOGY—Frederick H. Meyers, M.D., Professor of Pharmacology, University of California School of Medicine, San Francisco; Ernest Jawetz, Ph.D., M.D., Professor of Microbiology, Chairman, Department of Microbiology, Professor of Medicine, Lecturer in Pediatrics, University of California School of Medicine, San Francisco; and Alan Goldnen, M.D., Professor of Medicine and Obstetrics and Gynecology, University of California School of Medicine, San Francisco. Lange Medical Publications, Drawer L, Los Altos, Ca. (94022), 1968. 692 pages, \$8.00.

There is something very special and satisfying about a book produced by Lange Medical Publications. The characteristic double-columns of print of the larger volumes are pleasing to the eye, and the concise detailed information that packs the pages provides an extraordinary amount of detail. Useful and original compilations of data ensure the value of these books as reference works, and the usually flowing style of writing allows easy reading.

This review of pharmacology provides full measure of these excellent qualities, and the multiple authorship has been welded into a homogeneous continuum. The prevailing attitude of scepticism directed at manufacturer's claims is a welcome approach that the authors have adopted to provide guidance in drug selection from the cornucopia of pharmacological products.

The coverage of topics is adequate and contains valuable features such as the excellent section on drug abuse and habituation, and the appendix tables listing the effects of drugs on common clinical laboratory procedures, and the drugs hazardous for use during pregnancy. An unevenness creeps into the policy regarding the completeness of bibliographical references which vary from superabundant (Chapter 60) to miserly (the chapters on antibiotics). Occasional statements are unnecessarily provocative and pass undocumented, such as "the claim that diphenylhydantoin causes pulmonary fibrosis has not been confirmed" (page 316).

The authors frequently indulge their interests in a personal way, as in the section on alcoholism, and fall repeatedly into the trap of straying from pharmacology into

technical therapeutics as in the over-detailed description of precautions to take during lumbar puncture (page 228). A contrasting, and more serious, fault is found in many sections where there is insufficient practical information to help the reader select a particular drug formulation: thus in the discussion on antacids, it would have been valuable to have contrasted the electrolyte contents of the alternatives listed, and in the discussion on digitalis more specific guidance should have been included on the advantages of different digitalizing and maintenance regimens. This book has to compete with the Lange text on Diagnosis and Treatment, and a contrasting approach to therapy should have been accorded to emphasize the pharmacological basis of drug selection: too often this text on Medical Pharmacology resembles its well-established competitor. Numerous examples of the inadequacies of this review could be cited: thus intravenous colchicine is not mentioned, the various available preparations of PAS are not detailed, and so on.

Some of the best chapters are those on drugs acting on the central nervous system; some of the poorer discussions are those where physiological principles should have been invoked as a basis for the pharmacological approach, as in the sections on shock and fluid balance which are both inferior. The most disappointing chapters are those on antibiotics, where descriptions of drugs are often inadequate (e.g., cephaloridine, gentamicin). Specific faults in these chapters could be mentioned, e.g., the advised dose of colistin (page 513) is inadequate; the chapter on penicillins fails to detail the precise advantages of the different preparations, and does not discuss the use of penicillinase; the dosage of intramuscular tetracyclines is not clearly stated. The chapter on Chemoprophylaxis is interesting, but it is surely misplaced in a text on pharmacology. The last two chapters in the section on chemotherapeutic agents are contributions on antiprotozoal and anthelmintic drugs, and are excellent.

Many other individual faults in this text could be cited in detail, but few are serious. Definite errors are not readily found, and the printing mistakes detected were limited to the mis-spelling of Sharpey-Schafer's name (page 231), the failure to include footnote 5 following Table 46-1, and the omission of the Chapter reference to RTF (page 505). A more serious fault is the tendency to include large diagrams which contribute nothing but length to the book, e.g., Figs. 6-1, 9-1, 37-1, 37-2.

The ultimate questions concerning this book are whether it was necessary, and who should buy it? Undoubtedly, it provides a very good guide to therapeutics, but it falls short of being an adequate reference book, which is a major requirement for any physician faced with the daily problems of practical drug dosage, indications, contraindications and side-effects. For the student or practitioner who already possesses the Lange series of texts on medicine and therapeutics, this new publication would be somewhat superfluous, since there are so many areas of overlap with the former books. However, if one finds Goodman and Gilman too indigestible, and Current Diagnosis and Treatment is not in one's library, then the \$8.00 that this review costs will be well-spent not only by medical students, but also by qualified practitioners who wish to own an excellent, readable and reliable guide to the application of pharmacology to clinical medicine. If the next edition contains more detailed, critical guidance to drug selection and more emphasis on the problems of contraindications and side-effects (preferably in tabular form), then it will surely come to meet as wide an ownership in personal libraries as any other text of practical pharmacology.

IRWIN ZIMENT, M.B., M.R.C.P.

THE SCHIZOPHRENIC SYNDROME—Leopold Bellak, M.D., and Laurence Loeb, M.D., Editors. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 879 pages, \$24.75.

Eleven years after the senior editor's last review of the schizophrenic syndrome, this even more authoritative and encyclopedic treatment of the subject with 20 chapters, 25 authors, and innumerable references is available. Bellak aptly begins his epilogue, "It is extremely unlikely that many a reader will have read through this volume from beginning to end. Even browsing or selective reading will have impressed on him the complexity of the schizophrenic syndrome. . . ." The significance of the public health problem represented by mental illness is brought home by the figures of an annual U.S. cost of 20 billion dollars, a daily patient census of 250,000 comprising one-fourth of all inpatients. Yolles points out that a minimum of 2 percent of persons born in 1960 will suffer an attack of schizophrenia some time during their lifetime and under certain conditions the maximum incidence is 6 percent. Bellak's basic philosophical position is attractive, namely that there is a group of schizophrenias, the syndrome (like inflammation) representing a final common path. Different etiologic factors play roles in different groups, and causation is multifactorial comprising genetic, physiological, psychological and social components.

To go on to some comment on content, Bellak presents in some detail including a long appendix his own research on ego function patterns in schizophrenia. This highly technical exposition, utilizing much jargon, of one worker's efforts to delineate clearcut syndromes, however worthwhile, seems inappropriate in a general reference book. A similar criticism applies to Alexander's personal, rather anecdotal case for non-drug somatic therapies including insulin coma, though his descriptions of procedures are clear. Most chapters, those on general biological, neurophysiological and psychological studies; on sociocultural aspects, childhood and adolescent schizophrenia, antipsychotic drugs, group psychotherapy, and hospital and community psychiatric approaches are all remarkably comprehensive in citing the vast literature in these areas, and thus are invaluable as sources of reference. However, these chapters suffer badly from lack of critical comment upon the work they review and from inadequate analysis and synthesis of the material. Often poorly controlled studies or mediocre papers are given as much space as excellent research or creative formulations, e.g., recent work on perception, cognitive control and evoked cortical potentials or on family dynamics. A refreshing contrast is Kety's lucid chapter, albeit a skeptical one, on biochemical hypotheses and studies. There are good sections on symptomatology, diagnosis and course, prognosis, rehabilitation and a commendable stab at discussing prevention. Bellak and Loeb are successful and interesting in their comprehensive discussion of psychoanalytic, psychotherapeutic and psychodynamic studies. They convey a flavor of the thinking and methods of Sechehay, Boyer, Rosen, Searles, Laing, Lidz, Arieti (but not of the classic work of Sullivan and Fromm-Reichmann).

This book is encouraging in documenting the increasing sophistication and scope of research in schizophrenia, the usefulness of drugs, and the importance of the development of community approaches to mental health. The schizophrenias remain one of medicine's and society's great unsolved problems. Though a superb reference work, the general reader might well feel confused and overwhelmed by *The Schizophrenic Syndrome*. [A more readable, critically analytic (and cheaper) volume, which I have had the opportunity to preview, is C. P. Rosenbaum's *Perspec-*

tives on the Schizophrenias. Phenomenology, Sociology, Biology and Therapy to be published early in 1970 by Science House, N.Y.]

GEORGE F. SOLOMON, M.D.

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ASSESSMENT OF CEREBRAL PALSY—Volume I (Muscle Function, Locomotion and Hand Function)—K. S. Holt, M.D. (Manchester and Rochester, U.S.A.); M.R.C.P. (London); D.C.H. (England), Senior Lecturer in Child Health, University of Sheffield. Lloyd-Luke (Medical Books) Ltd., 49 Newman Street, London, 1965. (The Williams & Wilkins Co., Baltimore, exclusive U.S. agents.) 214 pages, \$9.00.

Cerebral palsy, a manifestation of a formidable variety of causes which damage the brain, appears in several forms and with varying degrees of neuromuscular involvement. There may be other defects, i.e., hearing, vision, impairment of intellectual development and seizures. In order to plan treatment effectively and to measure progress, all clinical features must be repeatedly reassessed. How this can be done for the physical aspects of cerebral palsy is described in *Assessment of Cerebral Palsy*, volume 1, by K. S. Holt.

Changes in the functional status of the cerebral palsied child occur as a result of factors associated with growth and development as modified by the existing abnormal neurological state. Further modification occurs as a result of the therapeutic efforts applied. With increasing introduction of systems of therapy which claim to be of value in the treatment of this group of conditions, a means of assessment which is objective can be extremely valuable to the cerebral palsy worker.

In this book, Dr. Holt presents a step by step demonstration of how to evaluate the child with cerebral palsy, and how to record results of the examination so that they can be used for comparison from one time to another. There are a number of photographs to aid the reader in following the described techniques.

The book should be of particular value to physicians who are not trained in orthopedic evaluation; however, the systematic approach to recording the observed data can be of value to all other physicians and therapists who carry out the prescription of the physician in charge.

The text is well annotated with references which are listed at the end of each chapter.

Dr. Holt indicates that this is the first of two volumes concerned with assessment of cerebral palsy, with the second volume planned to cover the assessment of sensory and intellectual factors. If the second volume is as good as the first it should be a valuable addition to the library of anyone concerned with the care of the cerebral palsied child.

PETER COHEN, M.D.

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SYMPOSIA ON RECONSTRUCTIVE PLASTIC SURGERY AND ON SURGERY OF THE HAND—1. *Reconstructive Plastic Surgery*—John Marquis Converse, M.D., Guest Editor; 2. *Practical Surgery of the Hand*—Martin A. Entin, M.D., Guest Editor. (Reprinted from *Surgical Clinics of North America*, Volume 47, Number 2, April 1967, and Volume 48, Number 3, October 1968.) W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 534 pages, \$15.00.

This volume is a reprint of two previously published issues of the *Surgical Clinics of North America*, well bound in an attractive hard cover.

The first part, edited by J. M. Converse in April 1967, contains two articles of basic studies, one on the biomechanical properties of skin, the other on histocompatibility. There are six articles on various aspects of reconstructive surgery for deformity following burns. The remaining five articles are on various aspects of hand surgery, as seen by the plastic surgeon.

The second part, reprinted from October 1968, is edited by Martin Entin of Montreal and is based upon lectures given by a group of foreign surgeons. Much of it is basic, some is repetition of the same material presented by these authors on other occasions, as would be expected in such a course of postgraduate studies. Fortunately, the inclusion of two orthopedists, Kaplan and Swanson, and of Verdan, who is primarily a general surgeon and who writes on fractures of the scaphoid, has prevented the issue from giving the reader the impression that surgery of the hand is solely within the province of the plastic surgeon.

Reprinting the two clinics and combining them in one volume makes for easy reference to the desired articles, especially by plastic surgeons. Others will miss the treatment of other topics which are a part of reconstructive surgery and of surgery of the hand.

JOSEPH H. BOYES, M.D.

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PSYCHOTHERAPY IN ACTION—D. Ewen Cameron, M.D. (Glasgow), D.P.M. (London), F.R.C.P. (C), Late Chairman of the Department of Psychiatry, McGill University, Psychiatrist-in-Chief, Royal Victoria Hospital, Research Professor of Psychiatry, Albany Medical College, and Director, Allan Memorial Institute of Psychiatry. Grune and Stratton, Inc., 381 Park Avenue South, New York, N. Y. (10016), 1968. 228 pages, \$8.50.

Some books, regardless of the quality of their contribution, immediately establish themselves as part of the mainstream, as representative of a point of view which, while perhaps contested, is broadly shared at a particular time. They address themselves to issues of recognized relevance in language (and with methods) that are commonly accepted. There are other writings, instead, which clearly have a very individual stamp and express mainly the author's special position. *Psychotherapy in Action* by the late D. Ewen Cameron, for many years the chairman of the Department of Psychiatry at McGill University, belongs to the latter group.

The book which describes basic psychotherapeutic approaches and may be looked upon as a short text on this subject, is mainly a distillate of the author's personal experiences and an expression of his particular convictions. It gives only very few references from the very large literature on psychotherapy and those which are cited would not generally be regarded as the classic papers in the field. Psychoanalytic authors largely are avoided.

Cameron's position is eclectic and represents a personal blend of views and approaches derived from Meyerian psychobiology and from conditioning. Psychoanalytic concepts are mentioned only very briefly and often in order to be quickly dismissed. Transference is said to be operative "only in a limited number of cases" and the Oedipus complex is regarded as an anachronism which has been surpassed and left behind. A chapter is devoted to "uncovering," but the emphasis is placed primarily on verbal "desensitization" (the process by which the affective response to certain emotionally loaded situations or ideas gradually is deconditioned) and to adaptive "problem-solving." Emphasis is also given to the use of the tape recorder in psychotherapy and to the value of playing back to the patient portions of earlier therapeutic sessions, a modification which Cameron helped to promote.

The book essentially consists of three sections, a short initial one devoted to a discussion of basic premises, a longer central one dealing with fundamental psychotherapeutic techniques and a description of the usual course of events in psychotherapy, and a final one which re-

views the applicability of psychotherapy to the various clinical syndromes.

The style is clear and literate (e.g., "Basic premises are those deep convictions which move and shape, form and change every aspect of every culture that man has made"), although the presentation at times tends to be repetitive and a bit diffuse. There is a penchant for personal terminology which usually is not as helpful as the author apparently thought. For example, "intensification syndrome" is used to refer to "a set of integrated functions which come into operation whenever the individual is under stress." Here and there are a few curious items, in part perhaps due to the author's limited opportunity to edit and proofread the book. For instance, Rogers' psychotherapy is called directive (p. 46) and vitamin B₁₂ is considered an euphorizing agent (p. 61).

Some opinions are expressed on clinical matters with which many would disagree. He says, for example, "The so-called conversion hysteria has become quite infrequent in occurrence. . . . La belle indifference remains more of a clinical fiction than a reality."

In sum, the book cannot be considered a landmark in the literature on psychotherapy and suffers, in fact, from limitations imposed on it by a very personal viewpoint. However, it will find readers among those interested in psychotherapy, especially beginners, because it deals with basic issues simply.

PIETRO CASTELNUOVO-TEDESCO, M.D.

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PROGRESS IN HEMATOLOGY—Volume VI—Edited by Elmer B. Brown, M.D., and Carl V. Moore, M.D.; With 20 contributors. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 389 pages, \$19.75.

This is the sixth volume of *Progress in Hematology* since 1956 and ably complements Wintrobe's text, *Blood and Seminars in Hematology*. The leading paper is a 70 page review on immunosuppression, covering the entire field—current concepts, method of approach, transplantation typing, auto-immune disorders, etc. A 40-page section by Dacie on auto-immune hemolytic anemias brings up to date his 1962 volume on this subject. Greenwalt and Perry outline the use of human blood components and Rizza and Biggs focus down on the use of plasma fractions in hemophilia and von Willebrand's disease. There are chapters on the prevention of Rh hemolytic disease, and the clinical usefulness of iron chelating agents, intrinsic factor and other B₁₂ transport proteins, and the mechanism of thrombosis. The control of human hemoglobin synthesis in health and disease is presented in a very readable manner. Newer tracer techniques picture bone marrow mapping, spleen scanning and other procedures. The bibliographies are lengthy and references up to 1968.

This volume is a must for hematologists, investigative or clinical. It will be something of value to the blood banker, the organ transplant, pediatrician, obstetrician, isotopologist, clinical pathologist and internist.

WILLIAM F. LUTTGENS, M.D.

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PICTORIAL MANUAL OF NEUROLOGIC TESTS—Maurice W. Van Allen, B.A., M.D., Professor of Neurology, College of Medicine, University of Iowa. Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago (60601), 1969. 200 pages, illustrated by George Buckley, \$7.95.

This manual incorporates many clinical neurological examination methods illustrated with simple line drawings including the underlying normal and disturbed anatomical and physiological mechanisms. It includes both the clinical neurological examination of the adult and a special

section for the infant. The basis and possible clinical significance of common abnormal neurological signs and syndromes is related to altered structure and function. An additional section is devoted to special clinical diagnostic procedures including lumbar puncture, vestibular tests, evaluation of mental status, aphasia and altered consciousness.

The use of a weighted 256 cycle tuning fork shown on page 31 in doing the Weber and Rinne tests of hearing would be more correctly done with an unweighted 512 cycle fork (though a generous drug manufacturer continues to give weighted 256 cycle forks to medical students in recent years). Auditory and vibratory receptors in the eighth and fifth cranial nerves may be simultaneously stimulated by the weighted 256 cycle fork but not by the unweighted 512 cycle fork, avoiding confusion of stimuli for the patient. The use of an unweighted 256 cycle fork shown on page 66 to test vibratory perception would be more appropriately done with a weighted 256 or 128 cycle fork since the weighted fork enhances and prolongs the vibratory stimulus.

This manual will be useful for medical students, interns, residents, and practising physicians dealing with neurological patients to help them understand and carry out a more meaningful neurological examination and evaluation. There are a comprehensive index and short bibliography.

CHRISTIAN HERRMANN, JR., M.D.

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ACHALASIA OF THE ESOPHAGUS (MAJOR PROBLEMS IN CLINICAL SURGERY—Volume IX)—F. Henry Ellis, Jr., M.D., Ph.D. (Surgery), F.A.C.S., Consultant, Section of Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester; and Arthur M. Olsen, M.D., M.S. (Medicine), F.A.C.P., Consultant, Section of Medicine, Mayo Clinic; Professor of Medicine, Mayo Graduate School of Medicine (University of Minnesota), Rochester. (Volume IX in the Series Major Problems in Clinical Surgery, J. Engelbert Dunphy, M.D., Consulting Editor.) W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 221 pages, \$9.00.

This encyclopedic monograph on the often misunderstood disease termed Achalasia provides a fine reference text. The authors have had long standing personal experience and interest in esophageal problems and portray their knowledge in a forthright and intensively detailed manner. The chapters on pathogenesis, clinical features, and treatment of the disease are well organized, complete, and well documented. Some readers will find the coverage of motility studies of the esophagus in healthy and diseased states interesting and refreshing. Although this book is included in the monograph series of *Major Problems in Clinical Surgery*, it is well referenced and documented. The book is recommended as a detailed reference source.

EDWARD J. HURLEY, M.D.

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PHYSIOLOGY OF THE HUMAN KIDNEY—Laurence G. Weson, M.D., Professor of Medicine and Head of the Division of Nephrology, The Jefferson Medical College of Philadelphia, Philadelphia, Pa. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 712 pages, \$34.00.

The student of renal physiology will find in this new text on *Physiology of the Human Kidney* the most comprehensive body of reference material since that compiled by Homer Smith in 1951. Of special interest to the practitioners are chapters by Drs. Mulrow and Goffinet on the controversial role of the kidney on blood pressure control, (the renin-angiotensin system) and by Erslev on erythropoiesis. In addition, there are excellent chapters on the metabolic aspects of renal function.

Any student of renal physiology will find this book an important addition to his library.

JAMES HOPPER, JR., M.D.

THE PEDIATRIC PATIENT/1968—Coordinating Editor, Sarah R. Gustafson, Ph.D., Consultant, Hoffman-La Roche Inc., Nutley, New Jersey; Consulting Editor, David Baird Coursin, M.D. F.A.A.P., Director of Research, Research Institute, St. Joseph's Hospital, Lancaster, Pa. J. P. Lippincott Company, East Washington Square, Philadelphia, Pa. (19105), 1968. 317 pages, \$8.00

This is the sixth annual review of advances in pediatrics. Like its predecessors it was edited by Dr. Gustafson and Dr. Coursin, published by Lippincott and has been quite widely distributed among practicing physicians as a gift from Hoffman-La Roche Inc. The three major topics covered in the 1968 edition are Enzymes in Health and Disease, Selected Topics in Neurology and Antimicrobial Therapy Updated. The remaining three chapters deal with orthopedic problems, progress in immunization and finally one called Miscellany in Brief. The latter devotes two or three pages per topic and deals with several dozen totally unrelated items such as the Clumsy Child, Gestational Age by Neurologic Examination, Therapy of Port Wine Angiomas, etc. Each of these brief topics typically summarizes three or four recent articles in the pediatric literature or deals with a topic presented at the Academy of Pediatrics meetings.

The longer chapters provide a considerably more complete review of the subject tackled and a respectable bibliography. The chapter on Neurology, for instance, is further subdivided into four topics dealing with the infant at neurologic risk, the minimally brain damaged child, intracranial tumors and Wilson's disease. The chapter on Antimicrobial therapy, as the chapter subheading promises, updates the current usage of the older antibiotics and deals with some of the newer antimicrobial agents. Many of the references in this as well as in other chapters are mostly from recent review articles rather than from original publications.

This volume will probably find its greatest usefulness, as it is indeed intended to, as a review for the practicing physician both in general practice and in pediatrics who has not had time to keep up with current literature in the major journals. Several evenings reading will bring him up to date on a variety of unrelated but important pediatric topics. Most of the subjects discussed would have immediate application to the patients he sees daily.

M. GROSSMAN, M.D.

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SURGERY OF THE ADRENAL GLANDS—Lawrence W. O'Neal, M.D., Assistant Professor of Clinical Surgery, Washington University School of Medicine, Staff, Barnes, St. John's, Jewish, and St. Louis Children's Hospitals, St. Louis, Mo. The C. V. Mosby Co., 3207 Washington Boulevard, St. Louis, Mo. (63103), 1968. 295 pages, with 212 illustrations, \$19.50.

In the preface to this splendid volume on *Surgery of the Adrenal Glands*, the author indicates that the book is intended primarily for use by surgeons. This objective is admirably achieved. The text is well organized and every conceivable aspect of the information necessary to assist those operating upon adrenal cortical disorders is covered in not only a concise but also a precise manner.

The volume, published in 1968, has 295 pages and 212 illustrations, contained in 13 chapters. Two appendices describe normal laboratory values of various hormones in blood and urine and a discussion of those drugs which may affect the results of hormonal tests of various kinds.

The developmental anatomy of the adrenal glands is covered in the first chapter in considerable detail, while in the second and third chapters a description of the adrenal cortical hormones and adrenal medullary and sympathetic nerve physiology is presented.

In each of the subsequent chapters, contributed by experts in their fields, the details of management of Cush-

ing's syndrome, virilizing and feminizing states, primary aldosteronism, and pheochromocytoma, are presented in an extremely readable fashion. Adrenalectomy for breast cancer, and surgery for the sympathetic tumors of the adrenal gland, are brought up-to-date, and the results of surgical treatment are discussed in considerable detail.

Of special interest and clarity of presentation is the chapter on roentgenology of the adrenal glands. Here the use of descriptive illustrations is especially effective, and representative x-ray photographs of adrenal cortical disorders are presented in clear detail with splendid legends. To complete the entire spectrum of the surgery of adrenal glands, a chapter on anesthetic management for adrenal surgery is included, which seems to be especially valuable to the surgeon in the management of patients undergoing surgery for adrenal-cortical disorders. A chapter on the preoperative and postoperative management of patients with adrenal problems is likewise of great practical value.

The final chapter is devoted to a series of paragraphs which describe the basic and major steps in the operative techniques for various adrenal diseases of a surgical nature. It is unfortunate, however, that the illustrations which portray the techniques are so lacking in detail, are not particularly well drawn and are anatomically inaccurate in certain areas.

At the end of each chapter the author has included a lengthy bibliography; these references in themselves are of great practical value, adding significantly to the overall excellence of the volume. The editor and the various authors are to be congratulated on the detailed nature of their presentations and the thorough manner in which the material is covered. The book should not only prove to be valuable to those presently in the surgical residency teaching program but also should serve admirably as a ready and complete reference manual to the established surgeon.

ORVILLE F. GRIMES, M.D.

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ATLAS OF OTORHINOLARYNGOLOGY AND BRONCHOSOPHOLOGY—Walter Becker, M.D., Professor and Head of the Department of Otolaryngology, University of Bonn, Germany; Richard A. Buckingham, M.D., Clinical Professor of Otolaryngology, University of Illinois College of Medicine; Paul H. Holinger, M.S., M.D., Professor of Bronchoesophagology in the Department of Otolaryngology, University of Illinois College of Medicine; Gunter W. Korting, M.D., Professor and Head of the Department of Dermatology, University of Mainz, Germany; Francis L. Lederer, M.D., Professor of Otolaryngology, Emeritus, and Former Head, Department of Otolaryngology, University of Illinois College of Medicine. (Edited by Walter Becker, M.D.). W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 315 pages, 1258 illustrations, 774 in color, \$75.00.

This excellent book should be in the libraries of all of our medical schools and in all hospitals with a service teaching otolaryngology and bronchoesophagology. Its many fine color illustrations clearly demonstrate the various diseases encountered in Ear, Nose, and Throat practice.

The pictures of face and neck lesions show rather advanced stages of the disease process. It might have been of additional help to show less advanced stages of these lesions as an aid to early diagnosis.

The x-ray pictures that accompany many of the depicted lesions indicate how truly revealing well-taken x-rays can be, particularly in regard to the temporal bone.

This book is a valuable reference, not only for the otolaryngologist and bronchoesophagologist, but also for anyone who deals with diseases of the head and thorax, including generalists, internists, pediatricians, roentgenologists, and surgeons.

F. H. LINTHICUM, JR., M.D.

SURGERY OF THE ADRENAL GLAND—Frank Glenn, M.D., Lewis Atterbury Stimson Professor of Surgery Emeritus, Cornell University Medical College, Consultant to the Department of Surgery, The New York Hospital; Ralph E. Peterson, M.D., Professor of Medicine, Cornell University Medical College, Attending Physician, The New York Hospital; and Henry Mannix, Jr., M.D., Clinical Professor of Surgery, Cornell University Medical College, Associate Attending Surgeon, The New York Hospital. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1968. 179 pages, \$10.00.

This brief volume, jointly written by two surgeons and an internist, summarizes the pathophysiology, diagnostic steps, and surgical management of aldosteronism, pheochromocytoma, and functional cortical tumors. Each topic is brought up to date concisely, with adequate graphs and illustrations.

The 12-page chapter on Surgical Approaches is disappointing in a book written primarily for surgeons. No mention is made of the chevron transverse upper abdominal incision which gives the ultimate anterior exposure. The lumbar approach is limited to the inadequate 12th rib excision, without mention of the far better, and hardly more difficult, 11th rib approach, or better still, the approach which excises the intercostal muscles from the upper margin of the 11th rib and allows its downward reflection. The posterior approach, a valuable one and not familiar to some surgeons and urologists, is described very briefly, without mention of positioning over the kidney rest, alternative directions for the incisions, use of retractors, and similar important details.

This book can be recommended, however, for surgeons and urologists who do adrenal surgery but have not kept up with diagnostic and operative management.

FRANK HINMAN, JR., M.D.

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CIBA FOUNDATION SYMPOSIUM—GROWTH OF THE NERVOUS SYSTEM—Edited by G. E. W. Wolstenholme and Maeve O'Connor. Little, Brown and Company, 34 Beacon Street, Boston, Massachusetts (02106), 1968. 295 pages, \$12.00.

This book is a collection of 14 papers presented in four sessions at a symposium held in June of 1967. The sessions were entitled "Development of Specific Neuronal Connections" (five papers), "Development of Movement" (two papers), "Role of Chemically Specific Signals in the Development of the Nervous System" (three papers), and "Trophic Interaction, Peripheral and Central" (four papers). The numbers of papers devoted to the various sessions approximately represent the pages devoted to the various topics. The work presented is all on experimental animals and the usual modern techniques of electrophysiology, tissue culture, radioactive tracers, and electron microscopy are utilized.

The symposium was chaired by Sir John Eccles and all of the members of the symposium were well-known experimentalists.

A book of this kind is difficult to review because each of the 14 papers is an independent presentation and needs to be reviewed separately. At least several of the papers would relate to the work of most neurologists, neurosurgeons and neuropathologists. All of the papers are well edited, but must be studied carefully and individually to be appreciated and should be of general interest. If clinically-oriented physicians had participated more and related the experimental findings to clinical problems, it would be better reading for most physicians. As is usually the case, the more interesting points come out in the discussions among the participants of the symposium which are included. The illustrations are good to excellent. One cannot find a unifying theme to characterize all of the papers. Certainly many of the papers do not relate directly to growth of the nervous system as the title of the book would suggest.

LARRY W. McDONALD, M.D.



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BOOKS RECEIVED

Books received by CALIFORNIA MEDICINE are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.

ADLER'S TEXTBOOK OF OPHTHALMOLOGY (8th Edition)—Harold G. Scheie, M.D., Professor and Chairman, Department of Ophthalmology, University of Pennsylvania School of Medicine; Chief of Ophthalmology Service, Philadelphia General Hospital; Ophthalmologist, Senior Surgeon and Head, Division of Ophthalmology, Department of Surgery, The Children's Hospital of Philadelphia; Chief of Ophthalmology Service and Consultant, Philadelphia Veterans Administration Hospital, Philadelphia, Pennsylvania; and Daniel M. Albert, M.D., Assistant Professor of Ophthalmology, Yale University School of Medicine; formerly Associate in Ophthalmology, University of Pennsylvania School of Medicine, Philadelphia General Hospital; Philadelphia Veterans Administration Hospital, and Children's Hospital of Philadelphia, Pennsylvania. W. B. Saunders Company, Publisher, West Washington Square, Philadelphia, Pa. (19105), 1969. 509 pages, illustrated, \$17.50.

ARTHRITIS AND PHYSICAL MEDICINE—VOLUME 11 OF PHYSICAL MEDICINE LIBRARY—Edited by Sidney Licht, M.D., assisted by Herman L. Kamenetz, M.D., with 21 contributors. Elizabeth Licht, Publisher, 360 Fountain Street, New Haven, Conn. (06515), 1969. 521 pages, \$14.00.

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